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LABORATORY PEDIATRICS

CLINICAL PEDIATRICS

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BY

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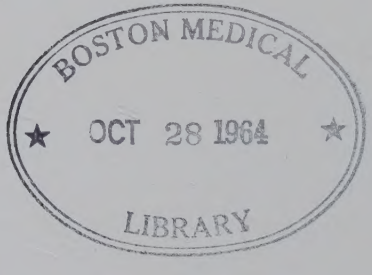

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PREFACE

The object of this book is to help the general practitioner to understand such pediatric cases as come under his care and require special aid from the laboratory to establish or confirm a diagnosis. It is not written for the pediatrician nor for the advanced laboratory worker. The attempt is made to concentrate on laboratory procedures of practical value and to omit those that have only a scientific value.

It is not a laboratory manual. The technic of a few of the newer procedures has been described, but the purpose of laboratory work in general and how to interpret the results have been emphasized. The man in practice should be equipped to do a routine urinalysis, determine the phthalein excretion, and do a concentration test. He should be able to do a simple blood count, and find the bleeding time and coagulation time. It is not difficult to count the cells and do qualitative tests for sugar and protein in the cerebrospinal fluid. Blood-sugar, urea and uric acid determinations, sufficiently accurate for clinical purposes, can be done in the office. The amount of laboratory work done by a practitioner depends on the time available. Most of the chemical and bacteriological methods call for considerable equipment, technical skill and experience. They are better left to those who have such equipment and skill.

It is hoped that the book may help to show how the laboratory may be of service, and point out the various ways in which laboratory examinations may bring additional evidence to "make assurance doubly sure," while emphasizing the fact that the results of laboratory investigation should never be looked upon as a thing apart, their interpretation being made in the light of the entire clinical picture which they help to complete. When thus interpreted, laboratory reports will always be helpful and often illuminating; when taken alone and without a background they may be misleading. If this book helps to point the way toward making a correct diagnosis more easily, more surely and more certainly, it will have served its purpose.

My thanks are due to my colleagues on the Pediatric Division of Bellevue Hospital and the Babies' Hospital, especially to Dr. Harry Bakwin, Dr. Ruth C. Sullivan and Dr. J. M. Brush. The chapter on serology is written by Dr. John P. Caffey.

JOHN D. LYTTLE

PUBLISHERS' ANNOUNCEMENT

The publishers take pleasure in presenting to the medical profession the series of monographs of which this volume forms a unit.

The many inquiries which reached them proved, in advance of publication, that the work should be in monographic form and clinical in its presentation.

The series when completed will, they believe, be the most useful for the audience for whom it is written, the general practitioner of medicine, that has been presented in its particular field.

The authors are all men of wide experience and, in the main, teachers. The combination makes the work authoritative and of the utmost service in a field which has been often termed a "therapeutic specialty."

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CHAPTER I

URINE

GENERAL CONSIDERATIONS

Importance of Urinalysis.—The importance of the examination of urine in infants and children is not sufficiently appreciated. One always demands information about gastro-intestinal function in any sick child. Kidney function is just as important. It is not necessary to have nephritis in order to have poor kidney function, and nephritis is so often present with good kidney function. The easiest and simplest way to get information about kidney function, whether the case is a well child, a cardiac or a pneumonia, is to examine the urine. No physical examination is complete without a urinalysis. It is true that you will examine many normal urines, just as you listen to many normal hearts. Neither can be neglected without harm to the patient.

Preservation.—Toluol, chloroform or thymol are the best preservatives. It should be remembered that chloroform is a reducing agent and should be driven off by boiling before tests for sugar are done. Urine to which thymol has been added gives a positive Heller's test for albumin.

For complete information on the physical, chemical and microscopic examination of the urine the reader is referred to any good laboratory manual. Urinalysis in infants and children differs in no way from that in adults. The significance of abnormal findings is somewhat different and what we shall attempt to do here is to discuss and interpret the abnormal findings in a general way and take up the diseases in which urinary changes occur.

Collection.—*Collection of Specimen from Female Infant.*—Cut square of adhesive 3 × 3 inches. In center of square make impression of ordinary test-tube opening by pressing mouth of tube against the adhesive. Cut 1¼ inch diagonal slits from each corner toward center of square. Cut 6 or 8 diagonal lines from center to circumference of

circle made by impression of test-tube mouth. On one side of square, cut out small semicircle, radius of ½ inch.

Bind edge of test-tube, if rough, with adhesive ½ inch wide.

Strip crinoline from surface of adhesive (this may be done earlier or later in procedure). Slip blunt end of test-tube through hole in center of square, having adhesive surface upward. Allow about ⅛ inch of tube to project at top. Fasten down points of adhesive to test-tube and cover points with adhesive ¼ inch.

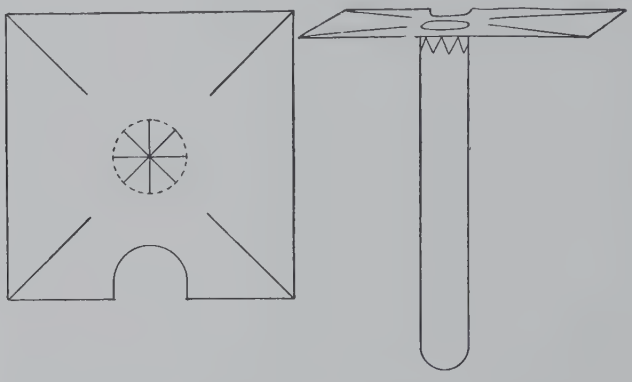

Fig. 1.—Device for Collecting Female Specimen.

Restrain child's legs 8 inches apart. Separate the labia, place tube over the urinary meatus. The semicircle in adhesive should extend downward leaving the rectum unobstructed. Smooth down lower side of adhesive, then upper side. Lastly fasten sides of square to overlap and completely cover the vulva.

Elevate head of bed 6 inches. Collect urine as soon as voided.

Collection of Specimen from Male Infant.—In collecting a specimen from a male infant a larger test-tube is preferable. The edge of the tube should be protected with a narrow strip of adhesive as described previously. The penis may be placed in the test-tube, and a band of adhesive fastened to the under side of the neck of the test-tube and brought up and crossed on top of the tube, the ends being fastened to the body above the penis. Legs should be restrained, head of bed elevated, etc., as described in the preceding.

Instead of applying the adhesive directly to the tube as above, the finger of a rubber glove may be attached to the test-tube by means of

a strong rubber band. The penis may be inserted through an opening made in the tip of the finger of the glove and the upper edge of this fastened firmly to the child by a band of adhesive. The latter method insures a better position of the test-tube for the collection of urine. Collect urine as soon as voided.

Characteristics in the Newborn.—The urine in the newborn presents peculiarities attendant upon the transition from intra- to extra-uterine life. The amount passed the first few days is variable, anywhere from 10 to 150 c.c. per day. It varies, of course, with the fluid intake. Occasionally no urine is passed in the first twenty-four hours. Toward the end of the first week, the output increases in amount up to 200 or 300 c.c. per day.

The concentration is comparatively high at first, 1.006 to 1.014, but after the fourth or fifth day it falls to 1.003 to 1.005, which is the concentration of the normal infant's urine.

During the loss-of-weight period the urine becomes cloudy and of a deep yellow color due to the presence of urates. Also at this time the urine is strongly acid.

A faint trace of albumin is always present in the first few days of life, and occasionally in the beginning of the second week. This must be regarded as physiological, and is probably due to congestion of the kidneys, since a passive hyperemia in the internal organs of the infant can last several days after birth. Another factor may be the uric-acid infarcts which occur in about 40 per cent of the newborn.

A transitory glycosuria is occasionally observed lasting a few days. This is said to be especially common where forceps have been used in the delivery.

A trace of acetone in the urine is occasionally noted in the newborn; it is probably due to partial starvation.

Indicanuria is frequently noticed on the third or fourth day. It is probably not pathological as it occurs under all conditions. It may be indicative of tissue destruction.

The sediment at this time may contain urates, uric-acid crystals, epithelial cells from the ureter, bladder and kidney, red and white blood-cells and a few hyaline casts. These findings are not to be considered pathological.

Amount.—In the healthy child the twenty-four-hour output varies with the fluid intake and the night volume is from one-quarter to one-half that of the day volume. Changes in the volume of urine and in the day and night ratio are due to nephritis, diabetes mellitus, and diabetes insipidus, circulatory failure, obstruction along the urinary tract, and fluid loss from diarrhea and vomiting.

ROUTINE CHEMICAL ANALYSIS

What a routine urinalysis should include depends somewhat on the history and physical findings in a given case. The following are the essentials:

Character and color, degree of turbidity, and amount of sediment
Specific gravity
Reaction
Glucose
Indican
Albumin
Acetone or diacetic acid
Microscopic examination

Tests for bile and other special tests can be done as indicated.

Quantitative work on casual specimens or when the diet is not accurately known is useless.

Reaction.—Normally, the reaction of the urine is acid due to the presence of diacid phosphates. An alkaline urine is due to an excess of alkaline phosphates and carbonates. For accurate determinations of urinary acidity it is best to do the hydrogen-ion concentration or use Folin's method. Direct titration with sodium hydroxid is not accurate.

The acidity of the urine is of interest when children are on certain diets, and in cases of pyuria and acidosis.

It is important to remember in these days of acid-milk feeding that organic acids are usually completely burned in the organism while inorganic acids are excreted as such. Greene has some interesting observations on the urinary changes following the ingestion of various acids and alkalis. Small amounts of hydrochloric acid are followed by

the appearance of casts and sometimes red blood-cells. These disappear two days after the acid is stopped. Alkali does not have the same irritating effect that acid does but Greene notes that large amounts of sodium bicarbonate are needed to bring about a definite alkalinization of the urine.

Determinations of urinary acidity can be done in the office by means of a few simple indicators and standard comparison tubes. There are many on the market and they are sufficiently accurate for clinical purposes. One can use bromcresol purple as a simple test. On the acid side of P^H6 the urine will turn greenish yellow, above P^H6 it will be purple.

Albumin.—Normal urine contains an amount of albumin too small to be detected by the ordinary tests. Addis in young adults found that in twelve hours not more than 30 milligrams of protein are excreted normally.

Too much has been written and too little is actually known about albuminuria in infants and children to make many definite statements here. For convenience we will exclude albuminuria due to nephritis and urological conditions. Those who examine many children are frequently puzzled by finding albuminuria with or without formed elements transient, intermittent or persistent over months and years in children who are not sick. Some of these come to the office for periodic examinations. Most of them have no special complaints. These albuminurias have been variously classified as "functional," "transitory," "cyclic," "toxic," "anemic," "benign," growth." Hooker and Post and Thomas have good reviews of the literature. Langstein found albuminuria in 12 per cent of children over five years of age. Hamill and Blackfan found albuminuria in 89 per cent of 124 children from eighteen months to fourteen years. Many other workers have found a high incidence of albuminuria in children. Calvin and others studied albuminuria in two groups of children. Group I was composed of children having no special complaints or illnesses, but coming from homes where hygienic conditions were very bad, improper diets, presence of foci were the rule, and malnutrition and anemia were common. Group II consisted of children in an orphan's home with medical care. Diets were balanced, foci of infection were promptly treated

and their lives were well regulated. The results are shown in the two tables.

DATA IN CASES PRESENTING ALBUMINURIA IN 520 CHILDREN EXAMINED (MORNING SPECIMENS USED) AND RESULTS OF REËXAMINATION OF SAME CASES OVER A PERIOD OF ONE YEAR

Group	Number of Children Examined	Boys	Girls	Age Range	Average Age	Percentage of Total Showing Foci of Infection	Total Percentage of Albuminuria	Percentage Boys	Percentage Girls
Group I.....	189	103	86	2–16	8	63	60+	45	70
Group II.....	331	181	150	6–16	11	0	15	10	20
6 months later							24	20	30
1 year later...							15	9	22

The microscopic findings were abnormal in less than 1 per cent of the cases.

Eighty per cent of the total albuminurias (60 per cent) showed evidence of malnutrition and foci of infection.

(Joseph K. Calvin, M.D., & Jacob Meyer, M.D., J. Am. M. Ass., June 12, 1926, Vol. 86, No. 24, p. 1821.)

Group I has a much higher incidence of albuminuria (60 per cent) than Group II (15 per cent). They used the ordinary heat and acetic acid test for albumin, and the cold acetic acid test. This last detects euglobulin, mucin and nucleoprotein. Twenty-six per cent of the urines examined and 50 per cent of those showing a positive protein reaction gave a positive cold acetic acid test. It seems that this nucleoprotein, euglobulin or mucin is the protein involved in many of these benign albuminurias. Other workers have found this to be so. There is no simple chemical method of separating these proteins. The only way to differentiate them accurately is to do the precipitin test.

Calvin *et al.* divide these albuminurias into:

1. Malnutrition albuminuria associated with anemia, underweight and foci of infection
2. Orthostatic albuminuria
3. Growth albuminuria

They say that some of the albuminurias in the malnutrition group clear up or improve when foci of infection are removed or treated, but they do not believe that these factors have any direct specific effect on the kidney. They assume the albuminuria to be one symptom of a

general systemic disturbance with faulty blood flow and blood volume resulting in impaired function of the body tissues. I think those cases of albuminuria with obvious foci of infection that clear up with treatment are in a different group. Any acute or chronic infection is a potential source of danger to the kidney, and albuminuria with or without good kidney function is one signal of change or damage. We quite agree that these conditions should not be emphasized to the patient, but that they should be observed by the doctor.

Lauener uses the term growth albuminuria and thinks that growth with its attendant phenomena is the most important factor in the albuminuria of the young. It is most frequent during adolescence, more common in girls and it is transient and benign.

Orthostatic Albuminuria.—There is no unanimity of opinion concerning the factors in the production of this condition. Other names for it are intermittent, postural, cyclic and adolescent. Orthostatic albuminuria is the term most commonly used, and by it we mean a condition in which the urine voided in the recumbent position contains no albumin, and the urine voided in the upright position contains, most of the time, variable amounts of albumin.

Calvin, Isaacs and Myer found in a group of 350 children in good hygienic surroundings, average age eleven years, sexes equally divided, albumin positive in 10 per cent of the boys and in 20 per cent of the girls. Of these albuminurias, 22 per cent (3 per cent of the whole group) were determined to be orthostatic in character.

Clinically, it is a disease of early youth, most of the cases being in the second decade. The children are thin, rapidly growing with long narrow chests and usually marked lordosis. They sleep too soundly and too long, but are tired always and there are evidences of vasomotor instability. Blood-pressure is normal, and there are no symptoms of kidney insufficiency. Very few cases are found after maturity.

The laboratory findings are concerned chiefly with the urine and kidney function.

A specimen collected in the morning before the patient gets out of bed is usually normal, contains no albumin or a very faint trace, no cellular elements or casts. The specimen collected after the patient has been up and active for an hour or so will show albumin in variable amounts and it is not unusual for a certain number of the cases to show

hyaline and granular casts and red and white cells. After lying down for an hour the urine is usually, but may not be entirely, albumin-free.

Most of the urinary protein in these cases is serum-albumin, but some of it is precipitated by acetic acid in the cold and is probably globulin.

The various kidney-function tests show normal results. The phthalein output while varying somewhat in the recumbent and upright positions is within normal limits. The Mosenthal or two-hour test shows normal variations in amount and specific gravity. The blood chemistry shows no noteworthy changes. Even in those cases with casts and cells there is no nitrogen retention, and plasma chlorids are normal. In spite of the protein loss the plasma proteins are normal and the A : G ratio is not disturbed.

Those cases with cells and casts should be treated as nephritis. Many questions concerning orthostatic albuminuria cannot be answered until a number of cases have been carefully studied and followed over a period of years.

Bence-Jones Protein.—Bence-Jones proteinuria is rarely found in infants and children. It occurs in cases of multiple myeloma, metastatic involvement of the bone-marrow, occasionally in leukemia, and it is sometimes associated with severe degrees of renal insufficiency.

It is difficult to identify by qualitative methods. The following test is the one most commonly used. The urine should be acidified with dilute acetic acid, and filtered if necessary. On heating the urine slowly in a test-tube, a heavy milky precipitate forms at 50 to 60° F. At 70° F. the precipitate lessens, and may disappear entirely at the boiling-point. As the urine cools the precipitate reappears.

Indican.—Opinions differ as to the value of performing tests for indican in the urine. It is supposed to indicate an increased destruction of proteins after a high protein diet, or to be the result of putrefaction in the intestinal tract in chronic constipation.

Glycosuria.—It is customary to divide glycosuria into those with hyperglycemia, and those with a normal blood-sugar. In infants and children we find a hyperglycemia and glycosuria in the following:

1. Diabetes mellitus
2. Large carbohydrate intake

3. Convulsions due to any cause (not constant)
4. Acute infection with fever
   Tuberculous meningitis
5. Increased metabolism, as hyperthyroidism and other endocrine dysfunctions
6. Intestinal intoxication
7. Disease of central nervous system
   Brain tumor, cerebral hemorrhage

A glycosuria without hyperglycemia is found in:

1. Renal diabetes
2. After drugs, as phlorizin, diuretics, etc.

These questions are considered in the chapter on glycosuria. Other reducing substances are found in the urine and among them may be mentioned pentose. A diet containing large amounts of arabinose-containing fruits (plums, grapes, apple juice) will sometimes result in pentosuria, but it can occur independently of the amount of pentose in the diet. When this condition is suspected the urine should be tested for pentose with Bial's reagent, or one of the other tests for pentose should be done.

Bial's Orcin Test for Pentose

Reagent:

Orcin 1 gm.
30 per cent hydrochloric acid 500 c.c.
10 per cent ferric chlorid 25 drops.
Keep in a dark bottle.

Boil 5 c.c. of reagent, add a few drops of urine (not more than 1 c.c.). With pentose a green color appears immediately.

Levulose is found in the urine after ingestion of large quantities of levulose, especially if disease of the liver is present; in diabetes levulosuria may coexist with glycosuria, and glucose in an alkaline urine may be changed to levulose. Levulose responds to most of the tests for glucose. In testing for it, Scliwanoff's test may be used or the polariscope.

Lactose may appear in the urine after the ingestion of large quan-

tities of milk or milk-sugar. It has no pathological significance. Mathews gives a simple method for differentiating it from glucose. The urine is fermented with a large amount of yeast. The glucose will be quickly fermented away, and its reducing action destroyed while the lactose remains unaffected.

Acetone, Diacetic Acid, Beta-Oxybutyric Acid.—Diacetic acid is rarely found in urine free from acetone and acetone may be present in the absence of diacetic acid.

Gerhardt's Ferric Chlorid Reaction for Diacetic Acid.—To fresh urine, add a few drops of a 10 per cent solution of ferric chlorid. This produces a yellow precipitate of phosphate. More of the reagent is added until all the phosphate is removed, and if diacetic acid is present, the addition of a few more drops of ferric chlorid will produce a Bordeaux red color. The red color disappears on boiling due to breaking up of diacetic acid. A reaction due to salicylates does not disappear on boiling. Acetonuria is present in infants and children in the following conditions:

1. Starvation
2. Cyclic vomiting and vomiting from any cause
3. Acute infections
4. Gastro-intestinal disease
5. After anesthesia
6. Diabetes mellitus
7. Ketogenic diet

Acetonuria can be considered as an evidence of disturbed metabolism, chiefly of fat and carbohydrate. It is rare for any sick child not to show acetone in the urine and the frequent association of upper respiratory infection and acetonuria has been brought out. It is present in some nervous disturbances.

Schloss has found that certain children are susceptible to ketosis due possibly to a deficient storage of glycogen. Much data on the mechanism of ketosis is being accumulated and will be discussed under acidosis.

Hematoporphyrin. — Hematoporphyrinuria (hematin without iron) is increased in cases of lead poisoning, and after certain drugs as trional and sulphonal. The urine is usually dark red. The simplest

way to examine for it is to use the spectroscope, but Garrod's test can also be used.

Hemoglobin.—Hemoglobinuria (the usual form of the pigment is methemoglobin) is distinguished from hematuria by the absence of red cells, and by the spectroscope. It occurs following destruction of red cells from any cause as burns, hemolytic poisons (phosphorus, carbon monoxid, phenol), scurvy, purpura, malaria, blood dyscrasia, and following blood transfusion. Paroxysmal hemoglobinuria occurs most often in syphilitic individuals, and the attacks are precipitated by cold.

Urobilin.—Traces of urobilin may be present in the urine of normal infants and children. If measured quantitatively the amount rarely exceeds 3 milligrams per 100 c.c.

Abnormal amounts of urobilin are found in:

1. Congenital and acquired hemolytic jaundice
2. Hemolytic anemia (malaria, hemolytic drugs, as benzol, lead)
3. After hemorrhage
4. Hepatic disease
5. Cardiac disease

There are various methods used in detecting abnormal amounts of urobilin in the urine. The spectroscope may be used, and Jaffé's or Schlesinger's tests are good for qualitative determinations. For quantitative work the method developed by Ellman and McMaster can be employed.

Urobilin determinations are of interest in following cases of hemolytic jaundice and hemolytic anemia and hepatic disease. In cardiac disease where the urobilinuria is due to liver congestion, and dysfunction attendant upon decompensation, Edelman has found a close relation between urobilinuria and the clinical condition. The more decompensated they are, the greater the quantity of urobilin in the urine. He believes that all cardiacs with a urobilinuria should be put to bed regardless of other clinical signs until the urobilin has become normal, and that the test should be used as a guide in the management of these children. Operative procedures should be avoided if urobilinuria is present, unless urgent. The procedure may have some prognostic significance since there is a sharp rise in urobilin prior to death.

Bile Pigments.—Bile pigments are not present in normal urine, but occur in cases with obstructive jaundice. Those cases of hemolytic jaundice show urobilin, but no bile pigments. There may be no change in the appearance of the urine, but usually it is greenish brown or dark brown in color. The usual qualitative tests can be applied.

Alkapton.—The urine in alkaptonuria turns black on exposure to the air, especially if made alkaline. The urine also reduces Fehling's solution, but does not ferment with yeast, and is optically inactive. It is probably an anomaly of intermediary protein metabolism resulting in the formation of homogentisic acid associated with inability to further catabolize this acid. Those who have this condition are otherwise healthy.

Chyle.—Chyluria always means that there is a direct communication between the urinary tract and the lymph channels. It is most often due to parasites, and Filaria is the most common. Cases have been reported due to Schistosoma, malaria, hydatids. In chyluria not due to parasites the condition usually disappears in the upright or reclining position.

The urine is usually milky in appearance and all the constituents of chyle are found: Sugar, fat, cholesterol, and lecithin, albumin, lymphocytes, and in the parasitic form the embryos of *Filaria bancrofti* are present.

Fat.—Small amounts of fat are present in normal urine and in pyuria. A large amount, a real lipuria, is present in cases of lipemia, and lipoid degeneration of the kidney. It most often occurs in diabetes and acute and chronic tubular nephritis. The fat may be extracted, or stained with Sudan III, or it may be found by using the polarizing microscope.

MICROSCOPIC EXAMINATION OF URINE

Urinary sediment may be examined after standing for some time in a sedimentation cylinder or after centrifuging. It is important that a fresh specimen be examined since in alkaline urines casts disappear quickly. No accurate idea of the sediment can be obtained from a urine that has stood twenty-four hours. We prefer centrifuging because it is quicker and we feel more certain that we are not missing anything. For comparison our method should be followed consistently.

Organized Sediments.—*Hematuria.*—The presence of microscopic or macroscopic blood in the urine calls for careful study to determine its origin and its significance. The conditions in which hematuria can occur will be merely tabulated here. Some of these will be discussed in detail in another part of the book.

I. Diseases of the kidney and genito-urinary tract
   (*a*) Most forms of nephritis, hydronephrosis, pyonephrosis, renal embolism, polycystic kidneys, renal tuberculosis, febrile albuminuria, "kidney irritation" with any acute infection
   (*b*) Anomalies of the kidney and genito-urinary tract, such as movable kidney, stricture
   (*c*) New growths
   (*d*) Lithiasis
   (*e*) Infections anywhere along the genito-urinary tract

II. Systemic diseases
   (*a*) Scurvy
   (*b*) Hemophilia
   (*c*) Purpura hæmorrhagica
   (*d*) Polycythemia
   (*e*) Leukemia

It also occurs after trauma, certain irritant drugs and after exercise. It has been reported as occurring with attacks of acute appendicitis and occasionally as a form of vicarious menstruation, and in parasitic infections.

Addis has shown that in normal young adults the average red blood-cell excretion was 65,750 per twelve hours varying from 0 to 425,000. In a series of normal children we have found the average red cell excretion to be much lower than this.

Pyuria.—Definition.—All workers agree that the urine of normal infants and children may contain pus-cells. Friedman and Mitchell, doing urinary leukocyte counts by means of a blood-counting chamber, found in 140 counts an average of 10 cells; 20 per cent showed no

cells, 90 per cent showed 20 or less. In children above two years, the count was higher (12 cells) in females than in males (6 cells). Catheterized specimens showed about the same number of cells as voided specimens. The volume and concentration of the urine were not considered. Addis found in young adults that white blood-cells were excreted at an average rate of 322,500 per twelve hours varying from 32,400 to about 1,000,000. Helmholz thinks that 2 to 8 cells per low-power field in uncentrifuged urine is not abnormal. Usually there is not much doubt as to whether one is dealing with a pyuria or not. When there is any question the clinical findings and repeated observation of the urine will make it definite.

Diagnosis.—Recent work by Chown, and by Schloss and Wilson, seems to indicate that the diagnosis of pyelitis so commonly made in infants and children is not justified by the anatomical findings. Most of the changes are found in the kidney and not in the pelvis. Only in the advanced stages of pyohydronephrosis is the pelvis of the kidney involved. The following is a convenient working classification of pyuria in infants and children:

I. Acute pyuria
   (*a*) Mild
   (*b*) Severe
      1. Diffuse infiltration
      2. Multiple abscess formation
      Fatal or recovery with scarring

II. Recurrent pyuria
   Recurring attacks of acute purulent nephritis associated with upper respiratory infection difficult to differentiate from

III. Persistent pyuria due to obstruction
   Anomaly
   Strictures
   New growths
   Calculi
   Neurogenic dysfunction (spasm of vesical outlet)
   Tuberculosis (rare)

Acute Pyuria.—The urine in the acute transient pyuria may have any amount of pus from a few cells up to a turbid urine with a heavy sediment of pus. Rarely a few red cells and casts are found. This type clears up promptly and completely in a short time, two to seven days, within three weeks usually, and it clears up regardless of treatment. Kidney function may be normal or show more or less diminution. Blood chemistry is normal or shows a moderate degree of nitrogen retention. The creatinin is rarely elevated. The uric acid is almost always up from 5 to 7 milligrams. The non-protein nitrogen is normal or slightly elevated. There is usually an acidosis due to ketosis.

In the second type of acute pyuria (severe diffuse or multiple abscess formation) the changes are more pronounced. If there is no blocking, the pus in the urine settles out to one-half or one-third of the volume. Casts and red cells are more frequent in this type and there are usually signs of poor kidney function. Nitrogen retention may be more marked; there is a low phthalein excretion and the disturbance in acid base equilibrium is more severe.

It is well to remember that in suspected cases of pyuria one should always examine the urine repeatedly. It is not at all uncommon to see a child acutely ill—toxic, and get urine which shows only a trace of albumin, a heavy reaction for acetone, and microscopically *numerous bacteria* and only a few scattered white blood-cells; twenty-four or forty-eight hours later, with a drop in temperature and relief of symptoms, the urine will be loaded with pus.

Recurrent Pyuria.—It is difficult to say when an acute pyuria becomes chronic. The important thing is that when a pyuria has not cleared up in from six to eight weeks or when it recurs with or without upper respiratory infection over a period of months or years, it should be investigated urologically. It must be kept in mind that the acute transient type of pyuria can relapse or recur with each fresh infection that the child gets. When the case is subjected to urological investigation we do not expect to find the pathology that we get in the other types of persistent pyuria. There is no way now that we can tell the difference between this type (recurrent suppurative nephritis) and the chronic persistent pyuria due to obstruction. While we hold no brief for the theory that these pyurias are due to focal infection, it is only

fair to treat or remove any obvious foci of infection in the effort to clear up a chronic or recurrent pyuria.

Persistent Pyuria Due to Obstruction.—The indications for a complete urological investigation are the same as for an adult. No one indication is enough but with a careful history and physical examination the following points or combination of points should make one think of a urological investigation:

1. Abdominal pain and colic
2. Hematuria unexplained by a nephritis or blood dyscrasia
3. Enuresis that doesn't yield to treatment
4. Indefinite abdominal tumor
5. Disturbed micturition
6. Persistent pyuria

In most cases where tuberculosis, renal tumors and calculi are suspected it is justifiable to do a complete urological investigation.

The routine we have been accustomed to use in working up these cases is somewhat as follows. After a careful history and physical examination with special attention paid to the history of infection, urinary symptoms, and foci of infection, the urine is examined carefully and repeatedly. Urine-cultures are made and the residual urine determined. The phthalein excretion, the concentration test, the blood-urea or non-protein nitrogen are done. A plain x-ray of the urinary tract is taken to rule out calculi and spina bifida occulta. A cystogram is also done to determine the contour of the bladder, to pick up, if possible, diverticulæ and to see if there is reflux up the ureters. Then cystoscopy, ureteral catheterization and pyelography are done. Specimens from each side are cultured and the urea is determined and if indicated a search for tubercle bacilli and guinea-pig inoculation are carried out.

Mucus is present in small amounts in normal urine, usually seen as small threads. Large amounts indicate irritation along the urinary tract.

Epithelial cells are found more frequently in urine from females than males. It is impossible to tell the origin of every epithelial cell found in the urine. In the urine of females most of the epithelial cells come from the vagina. These are large squamous cells with small round nuclei. Cells from the kidney are round or cuboidal with a large

vesicular nucleus. They are abundant in cases of tubular nephritis. Epithelial cells in the urine commonly undergo fatty degeneration.

Casts.—Casts are in general molds of the kidney tubules. They are present in nephritis and in cases with transient renal congestion or irritation. They may be absent in certain types of nephritis, and their presence does not make a diagnosis of nephritis. Usually casts and albuminuria go together. Casts will not be found in dilute or alkaline urines, even though they are being put out by the kidney. This is especially true of hyaline casts.

Cylindroids are broader and longer than hyaline casts, and taper out into a long tail. The significance of cylindroids is probably the same as that of hyaline casts. They appear in certain cases of chronic nephritis without much albumin. If they appear alone and do not persist they are not of importance.

Hyaline casts are the commonest variety of cast and are supposed to represent coagulated albumin in the tubules. They disappear rapidly in dilute or alkaline urines. They are seen in all types of acute nephritis, after anesthesia, in febrile albuminuria, intestinal intoxication, and after exercise. If they occur alone and do not persist, and are not accompanied by other clinical and laboratory signs of disease, they are not of much significance. In cases of advanced sclerotic or interstitial nephritis, a few hyaline casts are found.

Granular casts occur in all stages and forms of hemorrhagic nephritis, and in degenerative nephritis. They are rarely found in sclerotic nephritis. The granules are thought to be derived from tubular degeneration, and it is thought that when the granules are coarse, a severe grade of nephritis is present.

Blood, pus and epithelial casts are composed of a more or less transparent matrix with corresponding cells attached. Blood-casts are always found in glomerular nephritis with hemorrhage from the vessels in the glomeruli. Pus-casts are found in so-called acute pyelonephritis, and indicate severe kidney damage. Epithelial casts indicate parenchymatous desquamation.

Waxy casts are large refractile casts most often seen in advanced nephritis. According to Addis they develop from a cellular cast and degenerate into the broad granular cast. Addis found that when these broad waxy and granular casts predominate in the sediment, the blood-

urea concentration was more than 100 milligrams per 100 c.c. and the patients died in true uremia.

Fatty casts are seen in fatty degeneration of the kidney where the tubules are involved.

CRYSTALS IN URINE*

Reaction	Crystals	Shape	Color	Solubility				
				Heat. sol	Acetic	HCl	NH_4OH	KOH
Acid	Amorphous Urates		Yellow to Rose Red	+	+ Uric Acid	+ Uric Acid	–	–
	Uric Acid		Colorless Yellow to Brown	–	–	–	+	+
	Calcium Oxalate	Dumb bells Envelopes	Colorless	–	–	+	–	–
	Calcium Sulphate	Needles	Colorless	–	–	–	–	–
Neutral	Ammonium Biurate	Morning Star	Yellow Brown	– –	+ Uric Acid	+	–	–
	Di-calcium Phosphate	Needles Wedges	Colorless	–	+	+	–	–
Alkaline	Ammonium Biurate	Thorn-apple Morning Star	Yellow Brown	–	+	+	–	–
	Amorphous Phosphates		Light	–	+	+	–	–
	Amorphous Carbonate		Light	–	+ CO_2	+ CO_2	–	–
	Calcium Carbonate	Dumb bell	Light	–	+ CO_2	+ CO_2	–	–
	Triple Phosphates	Coffin lid	Light	–	+	+	–	–
	Neutral Magnes. Phosph.		Light	–	+	+	–	–

* This table has been prepared by Dr. James S. Brotherhood, to whom the author is indebted for permission to publish it.

Unorganized Sediments.—Uric acid or urates are common, especially in the more acid urines (or, in the case of ammonium urate, in ammoniacal samples), or those which have a high uric-acid content. They are usually without clinical significance. Associated with symptoms of stone in the urinary tract, they may suggest the material of the stone.

Phosphates.—Dibasic or tribasic calcium phosphates are without significance. Ammonium magnesium phosphate ("triple phosphate") deposits from ammoniacal urine. Its presence usually indicates bacterial decomposition (of urea) which may occur before voiding (bacterial invasion of the tract) or after voiding (poor preservation of sample). The excretion of phosphates is said to be decreased in nephritis.

Calcium Carbonate crystals may appear in alkaline urine. They are unimportant.

Calcium Sulphate is occasionally seen in very acid urine, without significance.

Calcium Oxalate has no definite pathological significance. Its chief interest relates to the tendency of calcium oxalate to form calculi. Vegetable diets increase the oxalate.

Hippuric Acid crystals occur infrequently.

Cystin crystals appear infrequently. "Cystinuria" is of unknown cause, is frequently hereditary, and may persist for a lifetime without clinical symptoms. Rarely, it may be associated with the formation of cystin calculi in the urinary tract.

Xanthin crystals are rare. They are occasionally associated with calculus formation.

Leucin and *Tyrosin* may occur, perhaps related to abnormal liver function, and especially to liver degeneration such as phosphorus poisoning and acute yellow atrophy.

KIDNEY FUNCTION TESTS

Many tests for kidney efficiency have been developed, and some of them are extremely useful to the clinician in diagnosis, prognosis and treatment. Their accuracy may be questioned, but properly interpreted they are of much help in getting the information desired. They should never be used exclusively, but should be interpreted as part of the evidence. And one must bear in mind extrarenal conditions such as cardiac disease, anemia, metabolic conditions which have an influence on kidney function.

The following tests are simple and can be applied to children. In young infants, none of the functional tests are satisfactory except, of course, blood chemistry determinations. And in children of the runabout age, results must be interpreted with caution.

Kidney-function tests may be divided into four groups:

1. A measured amount of a dye is injected, and the ability to excrete this dye in a given time is estimated.

2. The ability of the kidney to maintain normal levels for nitrogen waste, chlorids, phosphates, etc., is shown by a determination of these substances in the blood.

3. The ratio between a substance excreted in the urine and the level of that substance in the blood over a period of time.

4. The ability of the kidney to concentrate.

These tests can be made as complicated as you please. One test from each group will be described as simply as possible. Their technic is described in any laboratory manual.

Phenolsulphonephthalein Excretion.—A known amount of this dye is injected in the muscle and the urine collected one or two hours later. The urinary output does not affect the amount of dye excreted. Posture apparently does affect the output, more dye being excreted in the recumbent posture. This test throws no strain on the kidney, and this explains why different results are obtained from the same normal individual at different times. Variable amounts of kidney tissue are functioning at any one time unless a burden is put on the kidneys to throw all tissue into action.

Children will put out from 40 to 60 per cent the first hour, and 10 to 20 per cent the second hour. It is a good rough index of kidney function.

Hynson, Westcott and Dunning put out ampules of the dye and sets of standards for comparison with full directions for performing the test.

Blood Chemistry.—One of the chief functions of the kidney is to eliminate nitrogen waste. Urea determination on fasting blood is most commonly used as an index of renal function. It does not begin to rise until about three-quarters of the kidney tissue has stopped functioning. Creatinin is easily excreted by the normal kidney, and is the last nitrogenous constituent to go up in disease. The value and place of blood chemistry in estimating kidney function are discussed in the chapter on nephritis.

Urea Ratios.—Möller, McIntosh and Van Slyke and many others have studied the relation between urea in blood and urine in normal and

diseased individuals. Van Slyke and his coworkers review the history of this work and describe a method, the urea clearance test, for determining this index of kidney function. This method takes into account the various factors, body weight, volume of urine, etc., which affect the urea excretion. This test is satisfactory in adults, but there are too few figures available for children to draw satisfactory conclusions.

Concentration Tests.—There are many modifications of this test; but essentially they are combinations of the water test, a description of which is given on page 37 of Volume XIX of this series, and which is also known as the dilution test. The latter is of limited value without being modified in some such manner. The concentration test devised by Mosenthal is satisfactory. The normal kidney can concentrate, it can respond to various demands upon it by manufacturing a urine of high specific gravity. When the kidney is at rest and there are no solids to be excreted, it puts out a urine of low specific gravity, little more than water. The diseased kidney is unable to elaborate a concentrated urine and responds to the demands made upon it by putting out an increased amount of urine of low specific gravity. The following directions are given by Mosenthal in carrying out this test.

The usual diet should be given, but no food or drink after the evening meal. Measure the fluid intake.

8:00 A.M. Void urine and discard the urine.
8:00 A.M. Eat breakfast.
10:00 A.M. Void urine and place all in the labeled bottle.
12:00 NOON. Void and save urine as before.
1:00 P.M. Eat lunch.
2:00 P.M. Void and save urine as before.
4:00 P.M. Void and save urine as before.
7:00 P.M. Void and save urine as before.
7:00 P.M. Eat supper.
10:00 P.M. Void and save urine as before. All urine voided after 10:00 P.M. until 8:00 A.M. is to be placed in remaining one or two bottles and labeled 8:00 A.M.
8:00 A.M. Void urine and place in above bottle or bottles labeled 8:00 A.M.

The criteria for estimating the efficiency of the kidney by means of this test are:

1. The variation of the specific gravity in the different specimens of urine collected.

2. The maximal specific gravity of any specimen.

3. The quantity of night urine.

4. The concentration of sodium chlorid, urea, or total nitrogen in any of the specimens.

5. The total quantity of sodium chlorid, urea, or total nitrogen eliminated.

Normal Standard for Test Day for Renal Function

Maximum specific gravity	1.020
Degrees variation of specific gravity	9 (less if too little water is taken)
Volume c.c. of night urine usually	400 c.c. or less
Volume c.c. of night urine doubtful	400 to 725 c.c.
Volume c.c. of night urine distinctly abnormal	750 c.c. or more
Urea in any specimen	Normal if 2 per cent or higher; not necessarily abnormal if less
NaCl in any specimen	Normal if 1 per cent or higher; not necessarily abnormal if less
Total amount of urea and sodium chlorid eliminated in twenty-four hours	A measure of the quantity of proteins and sodium chlorid ingested Insufficient elimination must be judged by the level of urea and sodium chlorid in the blood and edema

These figures are for adults. We have not carried out the chemical determinations in children, feeling that sufficient information is given by the amount and specific gravity of the urine.

Composition of a Normal Urine

Volume (24 hours) 1500 c.c.

Constituent	Absolute Weight, Grams	Approximate Percentage
Water	1440.00	96.0
Solids	60.0	4.0
Urea	35.0	2.33
Uric acid	0.75	0.05
Hippuric acid	0.7	0.05
Oxalic acid	0.015	0.001
Aromatic oxyacids	0.06	0.004
Creatinin	1.0	0.07
Thiocyanic acid (as KSCN)	0.15	0.01
Indican	0.01	0.001
Ammonia	0.65	0.04
Sodium chlorid	16.5	1.1
Phosphoric acid	2.5	0.15
Total sulphuric acid	2.5	0.15
Silicic acid	0.45	0.03
Potassium (K_2O)	2.5	0.15
Sodium (Na_2O)	5.0	0.3
Calcium (CaO)	0.25	0.015
Magnesium (MgO)	0.30	0.02
Iron	0.005	0.0004

Influence of Purine-free and High Purine Diets

Nitrogen ingestion 10 grams daily

Urinary Constituents Determined (grams per day)	Purine-free Diet	Purine Diet (medium)	Purine Diet (increased)	Purine-free Diet
Uric acid nitrogen	0.09	0.14	0.24	0.07
Total nitrogen	8.9	8.7	9.1	8.8
Urea nitrogen ($+NH_3$)	7.3	7.1	7.1	7.05
Creatinin	1.57	1.49	1.51	

ALTERATIONS IN COLOR OF URINE

Color	Cause	Condition or Remarks
Nearly colorless	1. Large amount of urine excreted 2. Diminution of pigment	1. Much drinking. Nervous conditions, diabetes insipidus, etc.
Orange-colored	1. Small amount of concentrated urine 2. Increased pigment 3. Occasionally bile pigment	1. Hard muscular work. Fever 2. Fevers 3. Jaundice
Orange-colored Reddish-brown	Administration of rhubarb, senna, chrysophanic acid	(These turn yellow with acid, red with alkali; a normal color going red with alkali - phenolphthalein.)
Dark brown	Methemoglobin	
Red	1. Blood 2. Anilin dyes in sweets, etc.	
Port-wine	Hematoporphyrin	
Brownish-black	1. Melanin 2. Much hemoglobin 3. Alkaptonuria	1. Melanotic sarcoma. Darkens on standing, does not reduce Fehling's solution, gives greenish-brown precipitate with ferric chlorid. (Yields chocolate deposit.)
Greenish-black	1. Hydroquinon, carbolic acid, salol, guaiacol, resorcin, naphthalin, etc. 2. Bile	2. In old - standing cases of jaundice
Yellowish-green Green	1. Bile 2. Santonin	Jaundice (Turns red with alkali.)
Yellowish and milky	1. Pus 2. Fat as (*a*) emulsion, (*b*) droplets	1. Chyluria 2. Lipuria in advanced renal diseases
Greenish-blue Blue	1. Excess of indigo - forming bodies 2. Administration of methylene blue	1. Typhus (Violet with alkali; cuts off red and yellow in spectrum.)

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CHAPTER II

GENERAL CLINICAL PATHOLOGY OF THE BLOOD

A description of the methods and apparatus used in determining hemoglobin, counting red and white blood-cells and platelets and doing the ordinary staining reactions can be found in Volume XI of this series. In working up cases of anemia in infants and children and in the various blood dyscrasias where more complete information is desired, other more or less complicated laboratory procedures are done. Some of these will be considered here.

HEMOGLOBIN

Brown and Rowntree, Osgood and others have recently called attention to the number of widely different hemoglobin figures used as 100 per cent by various authors.

Osgood gives figures for red-cell counts, cell volume and hemoglobin on 137 healthy young men. From these findings he calculates the color index, saturation index and volume index. We know of no such complete and painstaking work on an equal number of normal infants and children.

Williamson gives figures for hemoglobin from birth to 15 years.

GRAMS OF HEMOGLOBIN PER 100 C.C. OF BLOOD IN PERSONS RANGING FROM ONE DAY TO FIFTEEN YEARS OF AGE (WILLIAMSON)

Age	*Grams*
1 day	23.2
2 to 3 days	22.8
4 to 8 days	22.1
9 to 13 days	21.25
½ to 2 months	18.33
3 to 11 months	13.7
1 to 2 years	12.55
3 years	13.1
4 to 5 years	13.6

Age	*Grams*
6 to 10 years	14.15
11 to 15 years	14.75

Von Reuss quotes various foreign authors all giving high, but variable figures for the first few days. From a study of these tables he concludes that race also influences the amount of hemoglobin in the newborn. Von Reuss thinks that there is a regular fall in the hemoglobin from birth and that the value normal to the infantile period (70 to 80 per cent) is reached in the course of the second or third week. Here again we are not told how much hemoglobin 100 per cent represents.

Lucas gives the following figures for hemoglobin in the newborn:

Results on Hemoglobin Estimates (Lucas)

Day	Number of Cases	Hemoglobin Percentage		
		Maximum	Average	Minimum
1	36	140	117	85
2	27	135	114	100
3	17	135	110	80
4	26	130	114	95
5	18	125	107	75
6	21	130	113	80
7	16	125	109	75
8	20	125	103	60
9	17	115	103	90
10	13	120	97	70
11	18	120	98	70
12	12	115	91	55

Methods.—For research accuracy, Van Slyke's oxygen capacity method is the best. According to Osgood and Haskins most of the common methods in use are inaccurate for one reason or another. Haskins has prepared a standard solution for the Salhi that has the right color and is permanent. When the Salhi pipet and graduated tube are accurately marked and the inside diameters of the graduated tube and the tube containing the standard solution are the same, results are obtained which check very well with Van Slyke's method. For ordinary clinical use the Salhi with solid glass tube standards is satisfactory. On most instruments 100 per cent hemoglobin is equivalent to 13.8 grams hemoglobin per 100 c.c.

HEMOGLOBIN PERCENTAGE EQUIVALENTS ACCORDING TO VARIOUS STANDARDS

Grams per 100 c.c.	Dare	Haldane	Newcomer Williamson	Oliver	Sahli	Tallqvist	Von Fleischl Miescher
6	43.6	43.5	36.5	40.0	34.8	38.0	38.0
7	50.9	50.7	41.5	46.7	44.7	44.3	44.3
8	58.1	58.0	47.4	53.3	46.5	50.6	50.6
9	65.4	65.2	53.3	60.0	52.3	56.9	56.9
10	73.6	72.4	59.2	66.7	58.1	63.3	63.3
11	79.9	79.7	65.1	73.3	64.0	69.6	69.6
12	87.1	87.0	71.0	80.0	69.8	76.0	76.0
13	94.4	94.2	76.9	86.6	75.6	82.3	82.3
14	101.7	101.4	82.9	93.3	81.4	88.6	88.6
15	108.9	108.7	88.8	100.0	87.2	95.0	95.0
16	116.2	115.8	94.7	106.7	93.0	101.3	101.3
17	123.5	123.1	100.6	113.3	98.8	107.6	107.6
18	130.7	130.3	106.5	120.0	104.7	113.9	113.9
19	138.0	137.6	112.4	126.7	110.5	120.2	120.2
20	145.3	144.8	118.4	133.3	116.3	126.6	126.6
21	152.5	152.1	124.3	140.0	122.1	132.9	132.9
22	159.8	159.3	130.2	146.7	128.0	139.2	139.2

RED BLOOD-CORPUSCLES

All the published figures show a high red-cell count in the newborn. Only infrequently are counts below 5,000,000 reported.

Lucas, in this country, gives the following figures for the first twelve days of life:

RESULTS ON BLOOD-CELL ESTIMATES (LUCAS)

DAY	NUMBER OF CASES	RED CELLS PER CUBIC MILLIMETER		
		Maximum	Average	Minimum
1	31	6,700,000	5,511,000	4,000,000
2	26	6,200,000	5,352,000	4,100,000
3	17	7,800,000	5,116,000	3,500,000
4	25	6,200,000	5,244,000	4,000,000
5	15	6,700,000	4,983,000	3,800,000
6	20	6,600,000	5,114,000	2,000,000
7	16	6,000,000	5,108,000	3,800,000
8	19	5,600,000	4,504,000	3,800,000
9	20	5,700,000	4,891,000	3,800,000
10	13	5,500,000	4,130,000	2,800,000
11	18	5,700,000	4,561,000	3,500,000
12	12	5,800,000	4,533,000	2,000,000

Von Reuss gives the foreign figures as follows:

"The number of red blood-corpuscles is relatively large in the newborn child, for there are, as a rule, more than 5,000,000 per c.c., and

lower values are rare. Sometimes more than 8,000,000 may be counted. In severe cases of icterus, Heimann found lower values—5,500,000 as against 6,500,000 in non-jaundiced infants. Gundobin found an average of 6,700,000 with variations between 7,500,000 and 5,000,000. Scibiades gives an average value of 6,980,000 and Biffi or Galli one of 7,000,000. Further high values are given by Perlin (6,100,000 to 6,200,000 on the first day), Bidone and Gardini (6,000,000). Takasu gives as average value only 4,679,000, but his estimates do not deal with infants less than four days. According to Viereck, the blood of male infants is richer in erythrocytes. The maximum count is usually reached on the second day less frequently on the third or fourth day. It then falls gradually, and reaches an average of 4,500,000 by about the fourth week."

HEMOGLOBIN, RED AND WHITE BLOOD-CELLS FROM TWO TO FIFTEEN YEARS (PERLIN)

YEAR	HEMOGLOBIN, PER CENT		RED BLOOD-CELLS, IN MILLIONS		WHITE BLOOD-CELLS	
	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum
2	58	78	4.75	5.60	8240	13,400
3	60	80	4.90	5.35	8900	11,600
4	70	84	4.00	5.50	8600	13,400
5	72	81	4.70	5.60	8800	11,200
6–10	74	84	4.20	6.00	7800	9220
11–15	78	88	4.80	6.00	7800	8900

Lippman's article in the *American Journal of Diseases of Children* is valuable for those who want detailed information on the blood changes in the newborn period. His charts show graphically the variations in the first two weeks.

All workers are agreed that there is marked variation in the size and shape of the red cells in the newborn, that the hemoglobin is not very firmly attached to the corpuscles and that hemolysis occurs more easily at this time. It is probable that the hourly variation in the number of red cells is greater at this age. Lucas found nucleated red cells in 52 per cent of all cases on the first day and only 5 per cent on the second day. Fifty per cent of prematures show normoblasts, immature red cells and eosinophils. In adults a diurnal variation in the number of red cells has been shown. No work in children on this subject is available.

Fragility or Resistance of Red Cells to Hypotonic Salt Solutions.—The best method is to prepare a 10 per cent saline solution. Use pure dry salt and neutral distilled water. From this make up solutions of different strengths varying from 0.9 per cent to 0.2 per cent with a difference of 0.02 per cent in each solution. About 5 c.c. of blood are taken from the vein (dry syringe and needle) and gently shaken in a flask with 3 drops of 3 per cent sodium oxalate. The blood is centrifuged and the plasma removed. One drop of the emulsion of corpuscles is placed in 2 c.c. of the salt solutions and shaken. After waiting several hours or centrifuging, it is noted in what strength saline hemolysis occurs and in what strength saline hemolysis is complete. Normally, hemolysis begins at 0.45 per cent and is complete at 0.34 per cent, and variations beyond these limits are not very uncommon.

At the time of birth the red cells of the infant have the same resistance as that of the mother. Up to the fourth day the resistance increases and then it decreases until about the tenth day when it reaches a constant level.

Since the resistance is most marked in jaundiced infants, there is no relation between hemolytic jaundice, when the resistance is diminished, and icterus neonatorum.

In acholuric jaundice hemolysis begin sometimes as high as 0.86 per cent and is complete at a point where normal cells would not dissolve.

Widal and others have found that certain cases of hemolytic jaundice show normal resistance with unwashed corpuscles but with washed corpuscles show an increased fragility. When the serum is added again to the corpuscles, a normal resistance is shown. It is thought that in these cases there is a substance in the serum which protects the red cells against hemolysis except in the normal range.

BLOOD VOLUME

A good method for estimating blood volume is that used by Bakwin which is a micromodification of the method of Keith, Smith, Belt and Whipple. A known amount of a non-toxic, slowly diffusable dye is injected into a vein, is allowed to circulate for a few minutes and a specimen of blood withdrawn. By determining the concentration of

the dye in the plasma, the plasma volume may be calculated. The total blood volume may be computed from the hematocrit reading.

In the first six months an infant doubles the quantity of blood and in one year the quantity is tripled.

Lucas and Dearing found that the volume of blood in the newborn varies from 10.7 to 19.5 per cent of the body weight, averaging 14.7 per cent. The plasma volume varies from 4.2 to 7.7 per cent of the body weight, averaging 5.9 per cent. In older infants the blood volume was found to be from 9.0 to 12.6 per cent of the body weight, averaging 11.0 per cent. The plasma volume varies from 5.7 to 7.8 per cent of the body weight, averaging 6.7 per cent. McIntosh working with the carbon monoxid method found the blood volume in infants to be about 77 c.c. per kilogram of body weight.

Marriott and Perkins found the blood volume in normal infants to be from 8.0 to 10.8 per cent of the body weight. Bakwin showed that the decrease in blood volume as the age increases is due to a diminution in the volume of the red cells.

Marriott found the blood volume in infants with marasmus to be lower than normal infants, while Bakwin found it to be higher.

Bancroft thinks that blood volume should be regarded not as an integral part of the body weight but as a physiological variable that is adjusted to the work required of it and to the size of the area which it occupies.

COLOR INDEX, VOLUME INDEX AND SATURATION INDEX

In determining these indices it must be borne in mind that the hemoglobin and red-cell count vary with age and sex. These calculations cannot be made accurately unless the hemoglobin and red-cell count of the age and sex groups are available for comparison. It is obvious, too, as Osgood points out, that the hemoglobinometers in common use, which have from 13.8 to 16.92 grams of hemoglobin equal to 100 per cent, are useless for these determinations.

The color index is obtained by dividing the hemoglobin percentage by the percentage of red cells. A red-cell count of 5,000,000 is considered 100 per cent and 100 per cent hemoglobin is: The number of grams of hemoglobin per 100 c.c. of blood calculated to a red-cell

count of 5,000,000 per cubic millimeter in the average healthy person of the same age and sex.

The average hemoglobin coefficient on 164 men (Osgood 137, Haden 27) is 14.73 grams with extremes of 12.5 and 17.5 grams. In Osgood's series 90 per cent of the hemoglobin coefficients are between 13 and 16.5 grams.

The color index indicates the amount of hemoglobin per cell.

The volume index is obtained by dividing the percentage by the volume of cells by the number percentage of cells. It shows the volume of the average cells in relation to the number just as the color index shows the amount of hemoglobin to the cell in relation to the number.

"Since the color index indicates only the amount of hemoglobin per cell and not the concentration," Haden has suggested a "third index which indicates directly the hemoglobin content per unit volume compared with normal." This he has called the saturation index. It is calculated by dividing the percentage of hemoglobin by the percentage of volume of cells, or simply by dividing the color index by the volume index.

A great deal of work on the normal hemoglobin, color index, and volume index standards for the newborn has been done, but almost no work on older infants or children. Haden's figures for 11 infants are shown on page 33.

"The red-cell counts vary from 3.40 to 4.57 millions, with an average of 3.96 millions. The hemoglobin varies from 14.4 grams per 100 c.c. to 20.1 grams per 100 c.c. The average is 17.73 grams. On the normal adult standard scale these figures are equivalent to 92 per cent for the minimum, 129 per cent for the maximum, and 112 per cent for the average. . . . The cell volume is an excellent check on the accuracy of the hemoglobin determinations.

"The color index and volume index are high in every case. The maximum volume index is 1.64, the minimum 1.10 and the average 1.43. The maximum color index is 1.63, minimum 1.14 and average 1.41. The saturation index shows the variation from normal, running from 0.96 to 1.04. The average is 0.99. The concentration of hemoglobin per unit of cells is thus normal. These figures show that the changes observed are all dependent on an increased volume of the average red cells in the newborn."

FIGURES ON HEMOGLOBIN, COLOR INDEX AND VOLUME INDEX STANDARDS FOR ELEVEN INFANTS (HADEN)

Age	Red Blood-Cells in Millions per c.mm.	Hematocrit Reading	Oxygen Capacity per 100 Per Cent	Grams Hemoglobin per 100 c.c.	Hemoglobin in Per Cent	Volume Index	Color Index	Saturation Index
11 hours	4.57	50	20.9	15.6	100	1.10	1.14	0.96
5 days	3.52	55	23.9	17.8	114	1.64	1.63	1.00
5 days	3.86	51	21.7	16.2	104	1.38	1.35	0.98
5 days	4.21	64	27.0	20.1	129	1.58	1.53	0.97
6 days	4.50	57	25.2	18.8	120	1.32	1.33	1.00
8 days	4.22	50	22.0	16.4	105	1.24	1.25	1.01
9 days	4.12	58	24.8	18.5	119	1.47	1.45	0.98
9 days	3.87	59	25.7	19.2	123	1.56	1.56	1.00
13 days	3.81	54	22.3	16.6	107	1.47	1.41	0.96
24 days	3.69	53	23.3	17.4	112	1.48	1.51	1.02
	3.40	43	19.3	14.4	92	1.32	1.53	1.02
AVERAGE	3.96	54	23.28	17.37	112	1.43	1.41	0.99

Haden also compared the red-cell count in sinus and peripheral blood in 6 cases. The counts were uniformly higher in the peripheral than in the sinus blood. The sinus counts averaged 3.64 millions against an average of 4.54 in the peripheral blood. Haden thinks the high individual cell volume might cause a stagnation in the capillaries which would give the higher count in the peripheral blood.

WHITE BLOOD-CORPUSCLES

There is always a leukocytosis in the newborn. Many workers have studied this, and their figures vary considerably. Lucas, in this country, gives the following figures:

White Cells per Cubic Millimeter from Sinus Blood (Lucas)

Day	Number of Cases	Maximum	Average	Minimum
1	31	30,000	19,200	6400
2	22	38,000	15,300	8400
3	16	20,000	11,100	7200
4	25	19,000	10,300	6400
5	17	14,000	10,900	4600
6	19	17,000	11,500	7400
7	16	21,000	12,100	7400
8	21	45,000	12,400	6400
9	20	23,000	12,600	6200
10	12	18,800	12,200	7600
11	18	17,400	12,700	6500
12	12	22,200	13,200	7000

Lippman found the average leukocyte count at birth to be 16,600 and at twelve hours 22,500, with a drop to 11,300 at forty-eight hours, and of 9500 at five days.

Lucas found the leukocytosis in the newborn to be due to an increase in the polymorphonuclears. After the first day the lymphocytes increase and the polymorphonuclears decrease, so that between the sixth and ninth days they are present in about equal numbers. The lymphocytes continue to increase, and at the second week they are up to 75 per cent. There is an increase in the transitionals up to 16 per cent, and also a wide variation in the number of eosinophils, 1 to 8 per cent. Myelocytes and mast-cells are sometimes present in the newborn period. Arneth, working with his method of arranging the cells according to the number of their nuclei and loops, found a definite "shift to the left," that is an abundance of young cells.

Counts in infants with dehydration fever are not different.

Lippman found wide variations in the differential counts. The lymphocytes and neutrophils became equal at forty-eight hours whereas in Lucas' series they were not equal till between the sixth and ninth day. Lippman found an eosinophilia up to thirty hours after birth. Basophils are rare and the mononuclears and transitionals showed no increase.

Differential Count, Two to Thirteen Years (Benjamin)

Age, Years	Polymorphonuclears			Lymphocytes			Monocytes		Eosinophils	
	Max.	Min.	Norm.	Max.	Min.	Norm.	Max.	Min.	Max.	Min.
2....	42	30	36	61	47	54	7	2	5	3
3....	48	32	40	58	38	48	9	2	6	4
4....	53	33	43	43	33	43	9	3	8	5
5....	61	35	48	53	31	42	8	2	6	3
6....	62	38	50	52	22	37	8	3	6	3
7....	57	37	47	52	30	41	8	3	6	3
8....	65	37	51	46	24	35	8	4	6	4
9...	66	40	53	46	24	35	8	3	6	4
10...	64	40	52	40	22	31	8	2	6	4
11...	67	43	55	40	22	31	9	3	6	5
12....	68	44	56	41	23	32	8	3	7	4
13...	64	48	56	41	23	32	8	3	5	2

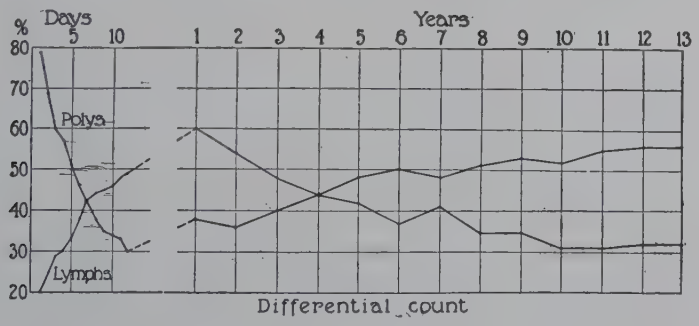

Fig. 2.—Chart Showing Differential Count from Birth to Thirteen Years.

PLATELETS

As in the adult, the platelet-counts in infants and children show a wide normal variation. For detailed information on this subject the reader is referred to the articles by McLean, Caffey *et al.* Most of the statements following are taken from this work.

In the newborn and in premature infants the platelet-count is fixed within narrower limits and has lower averages, 278,000 for the new-

born and 246,000 for the prematures. Lippman found 213,000 platelets at birth, with a drop to 170,000 in six hours. Lippman also found the platelets to be larger at this period. Counts in babies with icterus neonatorum were not different.

In normal infants and children the platelet-counts fluctuate between 200,000 and 550,000 with an average of 349,000.

In 19 cases of severe anemia McLean reports that only 3 showed a low platelet-count.

Removal of the spleen in normal children was found to cause a slight increase in the platelet-count.

In 173 cases of acute infection there was no significant alteration in the number of platelets. This is in contrast to adults where certain changes in the platelet-count are said to occur in infections.

COAGULATION TIME

There are several methods for doing coagulation time, all subject to a large error. The normal coagulation time is from two to eight minutes. Temperature, the size of the drop, the admixture of tissue juices and other factors affect the time of coagulation. For clinical purposes it is best to stick to one method. The error will be the same and the results will be comparable.

A good method is as follows: A number of capillary pipets are made 5 to 8 centimeters long. These are filled from an ordinary puncture wound and the ends are sealed with wax. The time is noted and one tube is broken every two minutes. When coagulation is complete the blood "strings out" at the break, whereas if there is no coagulation there is a clean break of the blood and tube.

According to Lucas and other workers, there is a definite prolongation of coagulation time in the first few days of life.

Coagulation Time in the First Twelve Days (Lucas)

Day	Longest (minutes)	Average (minutes)	Shortest (minutes)
1	29	15	16
2	23	18	10
3	24	15	10
4	32	16	10
5	26	13	5
12	15	10	5

Prothrombin (Thrombogen) Time.—To test the relative efficiency of prothrombin (or thrombogen) the method described by Howell is best; 5 c.c. of blood drawn by venepuncture is mixed with 0.7 c.c. of oxalate solution (1 per cent sodium oxalate in 0.9 per cent saline). The venepuncture must be done cleanly, and the syringe should be dry so that no hemolysis occurs. The blood is centrifuged at about 3000 r.p.m. for twenty minutes. The test should be run at room-temperature. Five drops of plasma are placed in five tubes (1.3 centimeters diameter, 6.8 centimeters high, with flat bottom) and to these are added in series, 1, 2, 3, 4, 5 drops and a 0.5 per cent calcium chlorid solution. The tubes are gently shaken and then tilted every few minutes. The time that it takes for the first clot to form, which is not dislodged by inversion of the tube, is taken to represent the prothrombin time.

Normal prothrombin time varies from six to fourteen minutes, with an average of nine minutes.

Howell found a prolonged prothrombin time in hemophilia, miliary tuberculosis, some cases of pernicious anemia, jaundice, benzol poisoning, and congenital stenosis of bile ducts.

He found an accelerated prothrombin time in some cases of leukemia and purpura.

Lee and Vincent showed that varying the number of platelets in an oxalated plasma will vary the prothrombin time. The fewer the platelets the longer the prothrombin time, yet cases with few platelets, such as purpura hæmorrhagica, have little disturbance in prothrombin time, and in hemophilia when the platelets are normal in number, there is a prolonged prothrombin time.

Bleeding Time.—This is always taken from the ear. The lobe of the ear is cleaned with alcohol and allowed to dry. Puncture is done in the usual way, about 2 millimeters deep, so that the blood flows freely and the time is noted. A piece of filter paper or blotting paper is used to absorb each drop of blood as it is formed. When drops no longer form, note the time. The normal bleeding time is from one to four minutes. When the platelet-count drops below 200,000, a prolonged bleeding time may be expected and the prolongation is in proportion to the drop in platelets. But it is quite possible to have a normal bleeding time with low platelets (86,000).

Sedimentation Time.—According to Lee and Minot this test is of no true diagnostic use. For methods, the article by Zukwin and Goodell on the "Sedimentation Rate of Erythrocytes" will be of help. Changes in sedimentation time are probably due to changes in albumin and globulin content of the plasma.

We have performed the test in numbers of infants and children with various diseases and our results agree with most published results. The changes are found in infections, cardiac diseases, nephritis and syphilis.

Character of the Clot.—Venous blood collected in a test-tube, unoxalated and undisturbed, will begin to retract and express serum shortly after coagulation is complete. This normally takes place within one or two hours, although it may not be complete for eighteen hours. Minot and Lee recommend that blood be kept in an incubator at 37° C. and observed at the end of twelve or twenty-four hours.

The retraction is said to be due to the blood-platelets. When platelets are greatly diminished the clot does not retract and with increased platelets the clot retracts quickly. But it is possible to have poor clot retraction with a normal platelet-count. This occurs in certain cases of anemia. In any event a poor clot means an abnormal blood, and if other conditions are right, hemorrhage is likely to occur. Another point to be observed in connection with the clot is its character. Normally, it is firm and tough. In purpura hæmorrhagica it is soft, mushy and friable, is easily broken up, and there are all degrees of this friability.

Another point to be observed is the completeness of the coagulation. Sometimes all of the red cells do not enter into the formation of the clot. They settle at the bottom of the tube and when the tube is tilted they will be seen to roll up the side of the tube.

Capillary Resistance.—If, when a tourniquet or a blood-pressure cuff is applied to the arm, a shower of petechiæ appear below the obstruction, it can be taken as an indication of blood-vessel changes. It is usually positive in the active stages of purpura hæmorrhagica but it is not diagnostic of this condition. We have seen positive tourniquet tests without any other indications of disease.

Bancroft, Kugelmass, and Stanley-Brown have published interesting work on the evaluation of blood-clotting factors in surgical diseases. They studied the bleeding time, coagulation time, prothrombin, anti-

thrombin, fibrinogen, platelets and platelet lysis in normal individuals, and those with various diseases and on various diets. From a study of these factors they calculate an index of blood-clotting function. They found an increased index (tendency to thrombosis and phlebitis) in certain infections and metabolic diseases, and a decreased index (tendency to bleed) in some hereditary conditions, blood diseases, liver disorders and infections. They were also able to prevent potential hemorrhagic disease of the newborn by prenatal treatment of the mother. It was also shown that the tendency to bleed or clot can be definitely influenced by diet. This work is very important not only in hemorrhagic diseases, but whenever operative procedures are in question. If further study bears out the value of these procedures as shown by the preliminary report, we have a means of getting important information at a time when such information is of use to the physician or surgeon. Lipins and globulins are said to be the sources of blood-clotting substances.

Icterus Index.—There are several good methods used in carrying out this test. That devised by St. George and Brown is a modification of Meulingracht's method, is simple and can be quickly performed. Killian has devised a permanent glass standard for use in colorimeters. The disk is inserted in one of the plungers and the comparison made against diluted or undiluted serum.

The standard solution is 0.05 part of potassium dichromate in 500 c.c. of distilled water with 2 drops of sulphuric acid. The depth of this color corresponds to an index of 1. A series of permanent standards of greater intensity of color are made and the comparison is made directly without dilutions.

Blood is collected by venepuncture in the usual manner, allowed to clot and then centrifuged. Needles and syringes must be dry. Clear serum is necessary, therefore blood should be taken before a meal. Any hemolysis makes the test of no value. The ingestion of eggs, oranges and carrots will deepen the color of the serum. This is another reason for taking fasting blood.

The normal index is from 3.5 to 5.5. According to Bernheim clinical icterus is always present when the index is above 15, and absent when the index is below 15. The zone of latent jaundice is therefore between 6 and 15.

This test gives accurate information only as to the depth of the

jaundice, that is the degree of bilirubinemia. It tells nothing as to the origin of the jaundice.

It is useful in diagnosis in the following conditions: In hemolytic anemia the index is above normal, while in secondary anemia the index is more often in the latent stage 7 to 10. It will indicate biliary obstruction and show whether the jaundice is increasing or decreasing. High indices are found in pneumonia, cardiac insufficiency, chronic sepsis, typhoid fever and malaria.

Van den Bergh Test.—As ordinarily used, this is a qualitative test for bilirubin in the blood. It can also be done quantitatively. The technic, as given by Van den Bergh, is as follows: 5 c.c. of blood is drawn by venepuncture, allowed to clot and centrifuged. Care must be taken that needle and syringe are dry and that no hemolysis occurs.

The reagent is a mixture of the following solutions:

Solution I: Sulphanilic acid 1; hydrochloric acid 15; water to 1000.

Solution II: 0.5 per cent sodium nitrate in water.

To 25 c.c. of solution I add 0.75 c.c. of solution II. The reagent should be freshly made as it does not keep for more than twenty-four hours.

To 1 c.c. of clear serum, 1 c.c of the reagent is added. A faint reddish violet to a deep purple color appearing within fifteen to thirty seconds, constitutes a positive indirect reaction.

To 100 c.c. of clear serum an equal volume of 95 per cent alcohol is added and the mixture centrifuged. To 1 c.c. of the reagent, 1 c.c. of the supernatant fluid is added. A color change in this mixture is a positive indirect reaction. The alcoholic dilution does not give the direct reaction.

Van den Bergh believes that there are two types of bilirubin which can be distinguished by this reaction. The type of bilirubin which is present in obstructive jaundice gives the direct reaction. Where the jaundice is not due to obstruction the indirect reaction only is found. Another difference in the two types is shown by the reaction with alcohol. The serum giving the direct reaction when precipitated with alcohol shows a definite absorption of the biliary pigments in the precipitate. The precipitate of serum which gives only the indirect reaction shows no absorption of biliary pigments.

Not a great deal of work has been done with this test on infants

and children. Grulee and Mebane review the literature and give results on 19 cases. All workers are agreed that in icterus neonatorum only the indirect reaction is found. In 2 cases of icterus neonatorum gravis a direct reaction was obtained. Grulee and Mebane found an indirect reaction in icterus complicating upper respiratory infections in 3 cases and in 1 case of jaundice following neo-arsphenamin (syphilis of the liver(?) bleeding time one hour and forty minutes, clotting time seventeen minutes). In 2 cases of acute catarrhal jaundice(?) the indirect reaction was obtained. (Case 1: No obstruction signs; jaundice since birth; postmortem findings, acute catarrhal gall-bladder. Case 2: five days history of clay stool. No acholic stools in hospital.) Because of his findings in the last two cases, Grulee raised a doubt as to the value of this test as a means of differentiating between obstructive and non-obstructive types of jaundice in infants and children.

In studying anemia and blood dyscrasia it is important to know whether the balance between blood destruction and regeneration is being maintained. The following findings are considered evidence of degeneration.

1. In red cells: Microcytes, changes in shape, achromia, basophilic stippling.

The Cabot rings and Howell-Jolly bodies may be taken as evidence of degeneration and also of increased production.

2. An increase of bilirubin in the blood (positive indirect Van den Bergh test) and an increase of urobilin in the stools.

The following findings are considered evidence of regeneration:

1. In red cells: Macrocytes, polychromasia, reticulation, normoblasts.

2. In white cells: Immature forms, young polymorphonuclears, myelocytes and megaloblasts.

Special Staining Reactions.—Oxidase Stain.—This will differentiate between cells of lymphoid and bone-marrow origin. Goodpasture's method (100 c.c. absolute alcohol, 0.05 gram sodium nitroprussid, 0.05 gram benzidin, 0.05 gram basic fuchsin) is commonly used, but there are others. The technic is the same as for Wright's stain except that weak hydrogen peroxid is used instead of water. The granular cells show deep blue-black granules which the lymphoid cells do not have.

Vital Staining.—The chief importance of vital staining is to demonstrate reticulation of red cells. This is a reliable index of bone-marrow activity. Brilliant cresyl blue (0.5 per cent solution in alcohol or water) is used. A drop of this is allowed to dry on a slide or cover slip, then a drop of blood goes directly on this stain, and a smear is made in the usual way and stained with Wright's stain as usual.

Blood-Grouping.—For those interested in the principles of the method, the original work by Jansky and Moss should be consulted. This is an important subject and a few general statements can be made. There is no such thing as a universal donor. It is not true that infants under six months can be transfused from the mother with safety. Dyke says that "there has been shown a variation in the agglutinating ability from serums of different persons of the same group as well as a variation in the ability of corpuscles of the same group to be agglutinated by the same serum."

It would therefore seem necessary to cross-match the blood before every transfusion, using fresh cells and serum. Furthermore, a donor being used repeatedly on the same case should be tested each time. The technic for blood-grouping is described in Volume XI, pages 30-33.

LEUKOCYTE COUNTS IN MISCELLANEOUS CONDITIONS

Physical Agents.—Sunlight and ultraviolet radiation cause a leukocytosis. The effect is immediate and increases with repeated radiations.

Woronoff and Riskin found in adults an individual variation of leukocytes during the day, the fluctuations amounting to 90 to 150 per cent. A leukocytosis after food was observed and also in starvation at the time food would have been taken.

Isaacs and Gordon found a leukocytosis and an increase in platelets after exercise.

No work like the above is available for infants and children, but it is quite likely that comparable changes take place. It is unlikely that these variations have much diagnostic or prognostic significance.

Recently a great deal of work has been done on the effect of various proceedings on the leukocyte count. Whitten and Martynoff found

a definite postoperative leukocytosis, mostly polymorphonuclear. It was highest at the fourth hour and was normal in from five to ten days. Mercury, some of the arsenicals, and yeast also induce a leukocytosis. In some forms of allergy and after the injection of milk there is a drop in the leukocyte count.

Meningitis.—A leukocytosis of from 10,000 to 50,000 with a polynucleosis up to 95 per cent is present in the disease. With an exacerbation there usually is a rise in the white count. During convalescence there is an eosinophilia. This holds true of infectious meningitis (meningococcus, pneumococcus and streptococcus).

Whooping-Cough.—A high white count is a fairly constant feature at the onset. Crombie found the average in 24 cases during the catarrhal stage to be 20,000 with a range from 7000 to 85,000. In the paroxysmal stage the average was over 22,000. With complicating bronchopneumonia the count may be extremely high. With improvement the white count goes down. The lymphocytes are increased relatively and absolutely, averaging 66 per cent and occasionally going as high as 85 per cent. Cabot and other workers report extreme leukocytosis, 185,000; 141,000 and one fatal case of 223,000.

Erysipelas.—A leukocytosis of 20,000 to 30,000 is usual in this disease, the increase being in the polynuclears. The total count falls about two days before the temperature drops. An eosinophilia during convalescence is common and a lymphocytosis (40 to 50 per cent) may persist for weeks.

Diphtheria.—A moderate leukocytosis due to an increase in the polynuclears is usual in diphtheria. With improvement the white count becomes lower. In the severe cases and those where there is a complication the leukocytosis will persist. A low white count with severe clinical signs indicates a poor prognosis. Diphtheria antitoxin injections usually cause first a leukopenia and later a leukocytosis.

Vaccinia.—According to Kato, there is a primary leukocytosis in infants under eighteen months of age, indicating a general reaction beginning on the third day, reaching as high as 13,300 on the fifth day. On the tenth day the count is practically normal. There is a secondary or true leukocytosis the time the lesion reaches its maturity on the twelfth day. The range is from 14,000 to 27,000. The decline is gradual, reaching normal the fourth week after vaccination. The dif-

ferential count shows no significant variation from normal, but some workers state that the first leukocytosis is due to an increase in neutrophils while the second is a lymphocytosis.

Variola.—Hayem found leukocytosis beginning the second or third day of the symptoms and increasing during suppuration up to 30,000. Hoffman reports a high leukocytosis at the fourth day usually with a high eosinophilia, a relative lymphocytosis and myelocytes. The changes were still present at the end of the sixth week.

Other workers have found an increase or a decrease depending on the stage of the disease. While there is no absolute argument as to the white-cell count in smallpox, it is safe to say then, there is a leukocytosis at some stage of the disease, and the increase is in the mononuclear rather than the polymorphonuclear cells.

Epidemic Encephalitis.—The red-cell count and hemoglobin show normal values.

There is considerable conflict of opinion as to the leukocyte count and differential in this disease. The Association for Research in Nervous and Mental Diseases found counts 4500 to 32,000, averaging 12,000 with an average polynucleosis of 70 per cent. Others report lymphocytosis or mononucleosis. It seems likely that there is no characteristic picture.

Anterior Poliomyelitis.—Draper states that during the first phase there is a constant and definite leukocytosis of 15,000 to 25,000 with a polynucleosis 10 to 15 per cent above normal.

Acute Rheumatic Fever.—Swift, Miller and Boots have followed the leukocyte curve in rheumatic fever over a period of time. What follows is a summary of their work.

In the monocyclic group, that is, patients with rheumatic fever and polyarthritis, who recovered without relapse, a definite leukocytosis of 9500 to 20,000 with polynucleosis in the initial stage was the rule. A rapid drop to normal or almost normal was noted following the institution of antirheumatic drug therapy with only a slight temporary rise when the drugs were discontinued.

In the polycyclic group (9 adults with polyarthritis and cardiac involvement) the curve shows a tendency to remain above normal for a much longer period than those in the monocyclic group. The effect of drug therapy was less marked. Following the institution of treat-

ment the fall toward normal was less noticeable and in several instances, even with the continuation of the drug, there was a marked rise following an initial fall. In most cases, there was a rise of from 4000 to 9000 following the discontinuation of the medication. In the continuous form, were those patients in whom the clinical manifestations were chiefly cardiac and those who had subcutaneous nodules. Most of these were children. Here the leukocytosis persists and drugs have little or no influence on the leukocytosis during the first four months. There is a transient fall to normal in the fifth month. A relapse is always heralded by a rise in the white count.

The differential count shows the increase to be in the polynuclears. There was a low-grade eosinophilia in three of the cases with chorea. There was no correlation established between leukocytes and residual valvular disease.

Scarlet Fever.—According to Bowie there is a leukocytosis beginning in the incubation period, reaching its maximum at the height of the severity of the disease. The count was from 15,000 to 40,000. In general, the leukocytosis varies with the severity of the disease, and a low count with severe symptoms makes the prognosis bad. The increase is in the polynuclear cells, 85 to 98 per cent. Myelocytes are almost always present. The eosinophils, low at the onset, increase after the third day and may be of help in the differential diagnosis. A mild anemia, lasting for a number of weeks, has been noted. This seldom requires treatment.

Typhus Fever.—Wilson states that there is usually a leukopenia followed by a leukocytosis with an increase in polynuclears, and a striking increase in large mononuclears.

Tuberculosis.—There is no characteristic blood-picture in any form of tuberculosis. There is, however, a leukopenia in the majority of cases of acute miliary tuberculosis. Cabot gives very low figures, below 1000 in 25 of 36 cases. A neutrophilic polynucleosis seems to be common. Cunningham, Sabin *et al.* believe that tuberculosis has a special predilection for stimulating monocytes and found a definite increase in these cells in tuberculosis.

According to Smith, in nearly all cases of generalized tuberculosis or disseminated tuberculosis of lungs, and in the later stages of tuberculous meningitis, there is a definite leukocytosis.

In pulmonary tuberculosis the white count is practically normal. Lymphocytosis is present in the early stages. With hemorrhage and with acute activity of process, a moderate leukocytosis with lymphocytosis occurs. And with a secondary infection a count as high as 20,000 may be expected with polynucleosis.

There is always an anemia present, its severity depending on the duration and activity of the process, and an accompanying secondary infection.

Measles.—It is generally believed that in measles there is a preeruptive leukocytosis. It is not known how early in the incubation period this develops, but it is usually present in the last few days before the eruption. This increase is due to a relative and absolute increase in the polynuclear cells. With the development of the rash there is a leukopenia, with a lymphocytosis of over 30 per cent; a leukocytosis at this stage indicates a complication. This fact would be useful in differential diagnosis, but there are cases on record of apparently uncomplicated measles when the leukocytosis persisted through the eruption. But as a rule, a leukocytosis is against measles and a lymphocytosis is for measles.

Influenza.—A leukopenia is characteristic of this disease, an average count being 6600, with some low counts around 3000. There is not much change in the differential count. With pneumonia, the count may go as high as 10,000 or 12,000, or it may remain low.

A polycythemia has been reported in a number of cases, 8,000,000 being the highest count recorded.

Typhoid Fever.—Coleman states that the leukocyte count is normal or moderately increased in the first week with a normal differential. Leukopenia develops as the disease advances, the greatest reductions occurring in the second week. The lowest count is in the severest cases. The average is between 4000 and 6000, but may go as low as 2000. There is a progressive increase in lymphocytes and decrease in polynuclears. Variations in the blood-picture are common, and the reaction to complications is not constant.

As to the count after perforation, Livingston and Squires analyzing the Bellevue Hospital cases for nineteen years found a leukocytosis after perforation in 15 per cent of the cases, a slight rise in 15 per cent, and a fall or an unchanged count in 70 per cent. So they conclude that

the opinion of a leukocytosis following perforation being a constant or usual finding, is erroneous.

Exanthema Subitum.—The typical blood-picture is a leukopenia with a relative increase in lymphocytes. A decrease in eosinophils has been reported.

Malaria.—A slight increase in leukocytes during and immediately following a chill, is followed by a leukopenia, an average count being between 4000 and 6000 with an increase in mononuclears.

The anemia caused early in the disease by the destruction of infected cells and also by hemolysis of cells not infected, is quickly compensated for by the response of the blood-regenerating organs. In the chronic and pernicious forms, a severe and persistent anemia can be expected.

German Measles.—About half the cases will show a leukopenia at its maximum, the third day after the eruption. The other half will show a moderate leukocytosis. A relative increase in lymphocytes and large mononuclears, of 40 to 55 per cent, is fairly constant.

Mumps.—A normal white-cell count or a mild leukocytosis with an absolute and relative lymphocytosis is the rule in mumps. A polynuclear leukocytosis sometimes goes with a complicating orchitis. Some workers have reported a postinfective eosinophilia at the tenth day.

Lobar Pneumonia.—A definite leukocytosis of 15,000 to 60,000, with a polynucleosis up to 90 per cent, is the rule in pneumonia. A count lower than 10,000 with polynucleosis less than 50 per cent is an indication of poor resistance. Myelocytes are commonly found. The total white-cell count drops at the time of the true crisis. A postinfective lymphocytosis and eosinophilia are present during convalescence. The fall in the leukocytes is slower than the drop in the fever.

Piney states that anemia is common in the postfebrile stage, but is never severe. In infants and children with pneumonia, it is our experience that severe anemia is frequently met with. In some cases the hemoglobin goes as low as 20 per cent with a red-cell count below 2,000,000. Repeated transfusions are necessary to control some of the cases.

According to Reimann there is a thrombopenia during the febrile stage, the platelets increasing after the crisis.

Bronchopneumonia.—A leukocytosis is the rule in this condition, counts averaging 18,000 to 20,000 with polynucleosis up to 80 per cent. As in lobar pneumonia, anemia is quite likely to develop.

Sepsis.—A variable leukocytosis with polynucleosis is the rule in various forms of sepsis. A count is of little value diagnostically or for prognosis, although a low count with severe symptoms is a bad omen. In infections with *Streptococcus viridans* and the colon group and with overwhelming infections of any sort, a low count can be expected.

An anemia goes with every infection whether prolonged or not. It is especially severe in streptococcus and pneumococcus infections.

Lues.—The relationship between syphilis and "blood diseases" is probably very important but most of our information on the subject is general and obscure. Severe anemia in infants with congenital lues without other causative factors can occur and often simulates the picture of von Jaksch's anemia. Zanca, in a study of 45 cases, found two main groups, a simple anemia where the red cells did not fall below 2,000,000 and a severe anemia. Some of the severe anemias approached the type of pernicious anemias or the pseudoleukemic anemias.

Tetanus.—There is no characteristic blood-picture in this disease. There is usually a definite leukocytosis during the spasms which is due entirely to the convulsions.

Osteitis Deformans.—Piney found no change in the total white-cell count but there was always a definite eosinophilia and basophilia.

The effect of x-ray on the hematopoietic system is a subject in itself. There is a leukopenia dependent on decrease of its neutrophils. Another effect is myeloid hyperplasia. Piney's articles will be of interest for those wanting more information on this subject.

The injections of nucleic acid have a temporary stimulating effect on the hematopoietic system.

Fractures.—A leukocytosis of 9000 to 17,000 usually follows a fracture within twenty-four hours. Fractures of the skull and multiple fractures show the highest counts. It is a polynucleosis.

ANEMIA

There is no very satisfactory classification of anemia in infants and it is doubtful if there will be one until we know more about the

etiology of these conditions. For convenience we will group them as primary and secondary.

Primary Anemias.—*Aplastic Anemia.*—Very little is known about the etiology of this condition which is brought about by failure of the blood-forming organs to manufacture blood-cells faster than they are destroyed.

The anemia is quite severe, hemoglobin going as low as 20 per cent or lower, red cells to one million. The smear shows the red cells to stain normally with little or no change in size and shape. Later achromia becomes a feature. Platelets are usually below 100,000, and white cells below 6000. Bleeding time is prolonged and coagulation time is normal. There are no evidences of regeneration.

Sickle-cell Anemia.—This is a familial disease occurring only in the Negro race (or those with an admixture of Negro blood).

In an active case there is definite anemia with red cells below three millions and hemoglobin reduced in proportion. The white cells range from 20,000 to 60,000 with a variable differential count. Large mononuclear phagocytes are present (5 to 10 per cent) with inclusions of red cells or fragments of cells. The diagnostic feature of the blood is the sickle shape of many of the red cells, up to 30 per cent showing this change. The forms taken vary a great deal, the cells may lengthen out to twice the diameter of a normal cell, or they may show as large or small crescents. Nucleated red cells are common and reticulation is increased. These changes have been found in bone-marrow cells. Latent sickling: Many individuals who show no abnormal cells in fresh blood will show sickling after the blood has stood for some time.

Secondary Anemia.—*Anemia Due to Blood Loss.*—There is a moderate reduction in the hemoglobin and red-cell count with a leukocytosis and normal differential, depending on the extent of the hemorrhage. In chronic blood loss the picture is variable, but the anemia is likely to be severe and reticulation is high. It is important to examine excreta and secretions for occult blood.

Nutritional Anemia.—The cases that fall into this group are those who have had an improperly balanced or insufficient diet (exclusive milk diet, etc.) plus bad hygiene over a period of time.

A variable anemia is present, the red cells ranging from four millions to one million with hemoglobin as low as 10 per cent. The white-

cell count is variable and not characteristic. Leukopenia is sometimes present, but the count may go to 20,000. The differential count varies with the age. The smear shows marked variations in the staining qualities, and size and shape of the red cells. Evidence of regeneration is usually present (reticulation, normoblasts). Immature lymphoid and bone-marrow cells are frequently seen.

Anemia with Acute Infection.—Sepsis, osteomyelitis, sinusitis, pneumonia, malaria, cardiac disease, empyema, tuberculosis and syphilis and almost any of the acute infections whether prolonged or not can set up an anemia which requires observation and treatment. Most of these cases are neglected in clinic and practice.

The picture is variable depending on the severity and length of the infection, and is the same as that described under Nutritional Anemia.

Anemia in Premature Infants and Twins.—Practically all premature infants and most twins develop a secondary anemia, and the severity of the anemia is proportional to the degree of prematurity. According to Merritt, prematures start with the usual high counts that are present in the newborn, but in six to eight weeks the hemoglobin may drop as low as 40 per cent with a red-cell count of around two millions. The smear shows normoblasts, young polymorphonuclears and myelocytes. Acromia is marked and there are definite changes in size and shape.

Chemical Poisons.—Lead, phosphorus, and bichlorid of mercury are at times the cause of a severe anemia in children and infants. Lead is the most common. The blood-picture varies according to the amount and character of the poison. Acute and chronic lead poisoning do not always cause a severe anemia. The usual picture is a moderate secondary anemia with basophilic stippling of the red cells.

Anemia with Nephritis.—In acute glomerular nephritis, a moderate secondary anemia is set up which clears up when the infection and nephritis have run their course.

In acute and chronic tubular nephritis (nephrosis) a definite secondary anemia develops and is a part of the picture. It varies with the nephritis.

In chronic diffuse and interstitial nephritis a much more severe anemia develops. The hemoglobin may go as low as 30 per cent with

red cells as low as two millions. The anemia is always present and is proportional to the degree of renal insufficiency.

BLOOD DYSCRASIA

Hemorrhagic Disease of the Newborn.—By this term we mean the spontaneous hemorrhages occurring in the first ten days of life. We do not include birth injury, sepsis, lues and severe secondary hemorrhages.

Bleeding from the bowel is most common. But there may be hemorrhage from the stomach, in the adrenals, into the cranial cavity or vertebral canal (although this is most commonly the result of injury at birth). And uncommonly, there may be bleeding from almost any part of the body—skin, mucous membranes, kidney, etc.

The resulting anemia is usually rapid and severe, depending on the extent and duration of the hemorrhage and the response of the hemopoietic system. There may or may not be jaundice. The platelet-count is normal.

The coagulation time is usually prolonged. Schloss and Comisky found it, in 10 cases, to be anywhere from three and one-half to ninety minutes.

The bleeding time is often prolonged, especially in those cases with cutaneous hemorrhages.

In some cases, Whipple found a deficiency of prothrombin. Whether the cause of this condition is a defect in the coagulation mechanism or lies in blood-vessel changes, it is dependent entirely on the age period. The babies that get well with proper treatment do not show any signs of a hemorrhagic diathesis at a later period.

Icterus Neonatorum.—As might be expected when so much is written and so little is known about the etiology of this disease or condition much of the laboratory data are contradictory. Whether clinical icterus is present or not, there is an increase in the bilirubin in the blood in the first few days of life. When the increase is enough to cause clinical jaundice with characteristic distribution the condition is called icterus neonatorum. We are not concerned here with sepsis or familial jaundice or icterus gravis. The significant laboratory findings are as follows: The urine is normal and contains no dissolved bile pigments, and the stools are not clay-colored. Some workers report a

higher percentage of occult blood in the stools of icteric babies than in the non-icteric. Those who believe the icterus to be due to a poorly functioning liver find that liver function tests show hepatic insufficiency. Other workers get contradictory results.

The red-cell count, the hemoglobin, the platelet-count in babies with icterus are normal. The increased resistance of the red cells in all babies at this age is said to be more marked in infants with jaundice and the prolongation in coagulation time normal for this period is said to be more marked in icteric babies.

The Van den Bergh test gives only the indirect reaction in this condition. This taken with the fact that there is no stenosis of the bile ducts, no bile pigments in the urine, absence of clay stools would seem to point to a hemolytic origin of the bilirubin. There is other evidence pointing to an increased destruction of blood as the cause of the icterus, yet since the resistance of the red cells is normal or increased and the outcome is quite different it does not belong to the group of diseases called hemolytic jaundice.

Hemorrhagic Diseases of Unknown Etiology.—Von Reuss mentions Buhl's disease or acute fatty degeneration in the newborn, Winckel's disease where cyanosis, jaundice and hemoglobinuria or hematuria dominates the picture and icterus gravis. Very little that is definite can be said about the etiology of these conditions. Laboratory and postmortem data are insufficient to draw any conclusions. Jaundice and hemorrhage are common findings in babies who die in the first few days of life. Organisms can be cultured from the blood in some of the cases and the clinical course of many of them is not unlike sepsis.

Hemophilia.—The positive laboratory findings in the disease have to do with blood coagulation.

The red- and white-cell count and the hemoglobin depend on the amount and frequency of the hemorrhages and the response of the hemopoietic system.

The platelet-count is normal or high, the bleeding time, the character of the clot when it does form, the capillary resistance, blood calcium, antithrombin, thrombokinase and serum proteins are all normal in this condition.

The prothrombin time and the coagulation time are definitely prolonged occasionally up to six or seven hours. This delay in prothrom-

bin and coagulation time can vary a great deal from time to time in each patient, and is not necessarily an indication of the severity of the condition.

Minot and Lee were able to demonstrate a qualitative defect or an increased resistance of the platelets which causes a delay in the release of the prothrombin. By adding a concentrated suspension of hemophilic platelets to recalcified normal plasma the coagulation time of this plasma was much longer than where a suspension of normal platelets was added. And by adding a suspension of normal platelets to hemophilic blood it was found to clot in normal time. These findings were confirmed by Davidson and McQuarrie.

Idiopathic Purpura.—*Symptomatic Purpura.*—Not a great deal is known of the etiology and blood-pictures in this group of purpura. By symptomatic purpura is meant a condition where there are cutaneous hemorrhages only and no bleeding from a mucous membrane. It may occur in the course of any of the infections, but especially in meningococcus meningitis and typhus fever. It occasionally occurs in tuberculosis. It may also be produced by bacterial emboli in endocarditis. Certain drugs and toxins may also produce a purpura. The iodids, mercury, arsenic, quinin chloral, snake venom and diphtheria antitoxin commonly produce such rashes. There is also a cachectic purpura occurring in old age or in the course of chronic nephritis and arteriosclerosis. Some purpuras occur from mechanical causes such as the application of tourniquets or after convulsions or the spasms of whooping-cough.

Except for the changes due to the primary condition, the blood-picture in symptomatic purpura is normal. The bleeding time, coagulation time and platelet-count are normal. But the capillary resistance is quite likely to be abnormal.

Under idiopathic purpura there are three groups of cases closely related to each other: Simple idiopathic purpura where the skin lesions are the only symptoms, Henoch's purpura which is accompanied by colic or other visceral symptoms, and arthritic purpura which is purpura accompanied by arthritis. It is sometimes called rheumatic purpura or Schönlein's disease, but its relation to rheumatism is doubtful.

Not much has been written about the laboratory findings in these conditions and the differential diagnosis is sometimes quite important.

According to Minot and Lee, the blood-platelets are usually normal, and, if anemia is present, sometimes increased. Occasionally, counts as low as 150,000 have been reported. Lower counts are rare. A simple posthemorrhagic anemia is sometimes found. Usually it is not severe. Normal coagulation, prothrombin and bleeding time is the rule, but occasionally a slightly delayed coagulation time is recorded. The clot is normal and the tourniquet test is sometimes positive.

There is usually no leukocytosis in the mild cases. In arthritic and Henoch's purpura there is usually a moderate leukocytosis, 10,000 to 15,000, with a polynucleosis; eosinophilia is rare. Since in visceral purpura there may be a slight fever and acute abdominal pain frequently, operations are performed on these cases.

Hematuria occurs in a number of the cases of Henoch's purpura and sometimes the signs of acute nephritis with impaired kidney function are present. Minot and Lee think the kidney lesions are produced in the same way as those in the skin and gastro-intestinal tract and are not truly nephritis. Blood in the stools is present in 50 per cent of the cases according to Minot and Lee.

Purpura Fulminans.—This is a rapidly fatal form of purpura occurring in children under ten years of age. The cutaneous hemorrhages are extensive, there is no bleeding from the mucous membranes, and the blood-picture is that of idiopathic purpura.

Polycythemia.—Lamson says that any condition in which the red-cell count is above 5 million may be considered polycythemia. Yet Osgood found in red-cell counts on 137 normal men the average to be 5.4 millions with 90 per cent of the counts between 4.7 and 6.1 millions and occasionally counts between 6.1 and 6.4 millions were found. Bearing this in mind the diagnosis of polycythemia should not be made so frequently.

Lamson divides the condition into two groups, a relative polycythemia where there is blood concentration and an absolute polycythemia where the total red-cell count as well as the number per unit volume of blood is increased.

Conditions that bring about a relative polycythemia are dehydration from any cause, injection of epinephrin or increased secretion of epinephrin from emotional stimuli, exercise and massage and increases in blood-pressure. Lamson lists many substances which are apt

to increase the red-cell count. Among these are tuberculin, strophanthin, pituitrin, phosphorus, opium, caffein, digitalis, carbon monoxid, arsenic and histamin.

Absolute polycythemia also occurs in a variety of conditions. Among these are chronic cardiac disease where there is interference with pulmonary circulation. Venous stasis, high blood-pressure and residence at high altitudes. An absolute polycythemia was first recognized by Vaquez and later described by Osler. Minot and Buckman have recently reviewed the subject. The disease is a hyperplasia of the erythroblastic tissue with excessive activity of the red marrow. It may also involve that part of the bone-marrow which produces leukocytes.

The red-cell count may range from 7 to 14 millions, and the hemoglobin is also up, but rarely high enough to give a color index of 1. Late in the course there may be an anemia. White cells are often increased, and a myelocytosis is sometimes present. Normoblasts are found and reticulation is increased. There is an increase in the fragility of the red cells. There is an increase in urobilin excretion, and in the number of microcytes in the blood. The basal metabolism is increased.

Infectious Mononucleosis (Glandular Fever).—This condition is rare in young children. Clinically there is fever, general glandular enlargement and large spleen. The laboratory findings by which it is differentiated from lymphatic leukemia are characteristic. There is little if any change in the hemoglobin, red-cell and platelet-count. The leukocytosis seldom exceeds 30,000 and this is due to an absolute and relative increase in the large mononuclear non-granular leukocytes. They run as high as 40 per cent.

Hodgkin's Disease.—From the many studies on the blood made in this condition, the conclusion is warranted that there is little specific in the blood-picture. A secondary anemia is commonly present, although the red blood-cells are not usually greatly reduced. Naegeli notes the hemoglobin seldom under 60 to 80 per cent. In a few cases, severe anemia has been noted: Fränkel and Much 1,140,000; Hirschfeldt 1,000,000, with hemoglobin of 20 per cent. On the other hand, where much cyanosis and dyspnea are present as a result of compression, high red-cell counts (6,000,000) and hemoglobin (125 per cent) have been reported by Naegeli.

Sir Humphrey Rolleston observes: "The white count does not show any constant or characteristic change. Usually leukocytosis is absent and there may be a leukopenia with a relative lymphocyte increase, especially, I believe, when the spleen is predominantly affected, a view shared by Weber."

Naegeli notes leukopenia particularly in the abdominal forms of the disease.

Various observers have called attention to certain phases they deemed characteristic, but these findings have, on the whole, not been demonstrated consistently enough to warrant their designation as typical of this disease. Bunting believed that the most striking feature of the white blood-cell count was a high percentage of transitional leukocytes in all stages, due possibly, he suggested, to the proliferation of the endothelial cells of the lymph-nodes. Though he believed the findings to be of diagnostic value, others (Perry, Pepper) have questioned their importance.

The latter author says: "A relative or even an actual increase in the mononuclear and transitional cells seems to be the most constant finding, but this is far from being pathognomonic of Hodgkin's disease."

Steiger thinks that the differential leukocyte count is characteristic of the stage of the disease, namely, a lymphocytosis in the early stage of lymphoid hyperplasia; a neutrophilia in the second stage; and, finally, a lymphopenia in the last stage with onset of fibrosis. It is very doubtful, however, that such a rigid grouping can be made. It is pointed out that it is usual for the disease to be present in different stages in different lymph-nodes and therefore unlikely that a clear-cut blood-picture should be present at any time, assuming the basis of the differentiation to be true.

In a later study, Bunting noted the absence of a single constant blood-picture in Hodgkin's disease. He believes, however, that two groups of cases can be distinguished:

1. Those of a duration of one year or less in which a normal or somewhat increased leukocyte count and a normal or slightly decreased percentage of polymorphonuclears are found.
2. Cases of more than one year's duration, showing sharp leukocytosis or a high percentage of polymorphonuclears.

Throughout the disease an increase of transitional leukocytes and a gradual decrease in the lymphocytes were noted. Piney remarks that "leukocytosis is almost invariable and there is no other disease (in which clinical evidence of infection is absent) in which a very high number of leukocytes can persist for so long a time." Naegeli makes a similar observation as to the persistent leukocytosis, reporting 6 cases from personal observation, with counts of 41,000, 45,000, 46,000, 48,000, 50,000 and 55,400, respectively. From the work published to date it seems fair to state that there is no characteristic blood-picture in Hodgkin's disease.

Agranulocytic Angina.—This condition occurs commonly in elderly females, but has been reported at the age of four and one-half years. The clinical picture is variable, but sore-throat, stomatitis, or dental infection is always present. The bacteriological findings are not definite. The change in the blood-picture, due to the action of an unknown agent on the bone-marrow, is characteristic. A moderate anemia may be present. Leukopenia (white cells, 1000 to 3000) is the rule with almost total absence of polymorphonuclears with a relative increase in lymphocytes, and an absolute increase in monocytes.

THE LEUKEMIAS

These conditions are considered in detail in the volume on blood and blood-building organs, of this series. Only the laboratory findings will be given here.

Acute Lymphatic Leukemia.—Hemoglobin and red cells vary with the degree of the anemia. Usually the anemia is apt to be quite severe. There are marked changes in the size, shape, and staining quality of the red cells, nucleated red cells are frequent, and reticulation is high.

The pathognomonic feature is the marked increase in the number of white cells, from 50,000 to 450,000. But this is subject to great variations. There are atypical cases in whom a leukopenia is marked, with a white-cell count of 1000. The increase in white cells is due almost entirely to the lymphocytes, these constituting up to 98 per cent of the total. Many of these lymphocytes are of the large immature type. An increase in leukocyte destruction is shown by the increase in the number of fragmented forms.

The platelets are always low, usually below 100,000, and associated with this is a prolonged bleeding time, and a soft non-retractile clot.

Chronic Lymphatic Leukemia.—This is not common in childhood, but any leukemia that lasts longer than three or four months may be called chronic. The laboratory picture is variable and is subject to remissions as is the clinical course. The red-cell count and hemoglobin tend to drop steadily. In contrast to the acute cases the white-cell count is higher, there are more small mature lymphocytes. Low platelet-counts are the rule, but not as low as in the acute type. The white-cell count is apt to vary from leukocytosis to leukopenia.

Acute Myelogenous Leukemia.—Clinically, this condition resembles lymphatic leukemia, but the blood-picture will differentiate. The anemia in myelogenous leukemia is usually just as severe and of the same type as in lymphatic leukemia, but the white-cell count tends to be higher. Counts of 200,000 and 350,000 are common. The increase is in the polymorphonuclear normal and immature forms, and in myelocytes and myeloblasts. The proportion of these cells varies with the course of the disease. Lucas notes that the early primitive cells of myelogenous origin frequently show few if any granules, and may look like large immature lymphocytes. This makes the differential diagnosis from acute lymphatic leukemia difficult. The oxidase stain, while not conclusive, will help to distinguish between cells of myelogenous and lymphatic origin. The bone-marrow cells show large blue-black granules, which are not seen in the lymphatic cells.

The platelets are not as low as in lymphatic leukemia, and some observers report high counts. The bleeding time and clot retraction vary with the platelet-count.

The laboratory findings in the chronic cases do not differ from those found in the acute form.

A critical consideration of aleukemic leukemia and the chloromata, which are closely related to the leukemias, will be found in Volume XI of this series.

ANEMIA WITH SPLENOMEGALY

Von Jaksch's Anemia.—Von Jaksch, Hayem, Luzet, Stillman and Cooley have described an anemia in infants and young children

variously known as *anemia pseudoleukemia infantum* (von Jaksch), *erythroblastic anemia of childhood* (Cooley), and *familial hemolytic anemia of childhood.* It is characterized by low hemoglobin and red cells, high leukocytosis, nucleated red cells continually present in abnormal numbers, enlarged spleen, liver normal or moderately enlarged, rickets not always present, and a prognosis which is bad, but not invariably fatal. At autopsy, liver and spleen show areas of hematopoiesis. Stillman and Cooley found that after splenectomy the nucleated red cells increased enormously, then fell somewhat, but were always increased. Cooley described the gross and radiographic bone changes in these cases.

The following summary of findings in 10 cases is taken from a paper by Wollstein and Kreidel.

"The presence of malaria, Leishmania, or any other form of parasite, can be definitely excluded because repeated examination of the blood, stools and spleen sections gave negative results. Five of the children were moderately rachitic, and one was syphilitic. None gave evidence of tuberculosis."

Pallor was the symptom stressed by the parents, and the color on admission was stated as sallow, lemon-yellow, or pale, but not jaundiced. The hemoglobin varied from 18 to 45 per cent, the red cells from 1,500,000 to 3,500,000, leukocytes from 9000 to 50,190 and the nucleated reds from 7 to 207 per 100 leukocytes. Fragility of the red cells was within the normal range. The platelets were normal in number except in one case where they were low for a time, but later rose to normal. Urobilinogen in the stools and urine was increased in the four cases in which it was studied. The icteric index was slightly above normal and an indirect Van den Bergh reaction was positive.

After splenectomy the blood gave the characteristic picture of a definite and progressive increase in the nucleated red cells, most of which were normoblasts. They ranged from 148 to 2016 per 100 leukocytes, or one and one-half to twenty times as many. Two of the patients survived splenectomy four years, and in both, one being still alive, the nucleated red cells became not only more numerous, but more immature. Thus the blood of one case showed normoblasts, macroblasts, many with segmenting nuclei, megaloblasts with polychromatic cytoplasm and mitotic nuclei. reticulocytes, and Howell-Jolly bodies. The

mature red cells show most marked poikilocytosis and anisocytosis, polychromasia and friability of the cell-bodies.

The hemoglobin and the total number of red cells remained below normal. The number of leukocytes diminished but little; the monocytes were increased for some weeks and then fell to normal.

The blood of three other patients on whom splenectomy had been performed for hemolytic jaundice, essential thrombopenia, and Banti's disease, respectively, was followed for three to seven years after operation. None showed the presence of nucleated red cells after the first few weeks, and never in such numbers as did these patients with von Jaksch's anemia.

Banti's Disease.—There is so much controversy as to whether this is a clinical and pathological entity that one hesitates to say anything about it. However, the syndrome described by Banti, in 1894, does exist. The clinical picture is variable and the laboratory findings are not much more definite. This condition is not common in the young.

Banti described three stages:

1. The anemic stage where there is an ordinary anemia, seldom severe (red cells 3 millions, hemoglobin 50 per cent). The red cells show moderate changes in size and shape, no normoblasts, and the white cells are normal. Moderate enlargements of the spleen and epistaxis are common. This stage may last one to three years.

2. The intermediate stage lasts about one year. Jaundice and enlargement of the liver occurs in this stage.

3. The ascitic stage develops gradually at about this time, the liver decreases in size and jaundice increases.

The blood-picture is not striking. The anemia is definite and the color index is low. Normoblasts are sometimes found and leukopenia is common with a relative lymphocytosis. There is usually a drop in the number of platelets, while the resistance of the red cells is normal. There is an increase in the urobilin of the stools and urine, depending on the amount of blood destruction.

Banti thought the disease was an infection with a predilection for the spleen, and suggested splenectomy. This is possibly of value early in the disease.

Many workers think this condition is merely a symptom complex,

or atypical cirrhosis of the liver, or is related to familial jaundice. The origin is still unknown.

Gaucher's Disease.—This is a rare condition of unknown etiology. It sometimes has a familial incidence, rarely runs an acute course; the usual duration of life after the diagnosis is made is from twenty to twenty-five years. It is characterized by large liver and spleen, a brownish color of the skin and, quite commonly, a brown pinguecula on the nasal side of the conjunctiva.

There may be a mild anemia, severe in the late stages. Leukopenia is rarely present and a low platelet-count is the rule. The platelets are not low enough to cause bleeding, although these cases do bruise easily.

The diagnosis is made by splenic puncture and the finding of typical Gaucher cells.

"The Gaucher cells have certain characteristics by which it is possible to recognize them either in microscopic sections or in films made from the surface of the organ. They generally measure from 20 to 40 micra in diameter, though occasional individual cells may be three to four times that size. Usually round or oval, they may be compressed into a polygonal form in large masses or they may appear to be drawn out into long strands or syncytial masses. The cytoplasm contains a network of fine wavy fibrils which run in the long axis of the cell and which give it a streaked appearance when cut longitudinally and a stippled look when cut transversely. Irregular colorless areas may be seen where the fibrils have been crowded apart by the accumulation of some substance which has not yet been identified but is said to be lipoid in nature. The nuclei are small and irregular and eccentrically placed. Cells with two or more nuclei, even as many as twenty-one, are said to be fairly frequent. Mitotic figures have not been described. Some of the cells may contain a certain amount of pigment." (Pool and Stillman.)

Hemolytic Jaundice (Acholuric Jaundice, Familial Jaundice).—Two types of this condition are usually recognized: the congenital type where there is a definite familial history, and the acquired type where heredity does not seem to be a factor. Some workers point out that not all the cases show complete pictures and that some of the cases are so mild or so well compensated that they escape diagnosis.

Yet these cases are capable of transmitting the disease, and since there is no family history these cases are said to be acquired. The clinical course and the laboratory findings in both types are essentially the same, but Piney states that since those patients with the acquired type do not transmit the disease we are justified in regarding it as being different from the familial form.

Clinically, the condition is usually discovered in early infancy, and a history of icterus neonatorum is frequent. The jaundice is usually mild except during an acute infection or a hemolytic crisis when all the symptoms are likely to be intensified. The anemia is usually mild. The spleen is almost invariably enlarged. Cholelithiasis is common in those who reach the fourth and fifth decades. There is not much disability, they are "more icteric than sick."

The anemia is not severe, the hemoglobin may go as low as 60 per cent with a red-cell count seldom below three millions. In acute exacerbations there may be a transient severe anemia.

The number of white cells is usually normal, but there may be a leukocytosis or leukopenia; occasionally a few myelocytes are found.

The stained smear shows definite changes in the red cells. Microcytosis is always present. Reticulated cells are found in all of the cases. In normal blood about 1 per cent of the red cells show reticulation, while in this disease the number is sometimes as high as 30 per cent. It is always high when the anemia is severe. Piney thinks there is a close relationship between the amount of hemolysis and the number of reticulated cells. He notes that during periods of intense jaundice the reticulated cells are increased, although the anemia does not necessarily increase. He, therefore, thinks that reticulation must be regarded as evidence of regeneration.

Polychromasia and nucleated red cells are frequently found, and occasionally nuclear remains, as Howell-Jolly bodies and Cabot rings, are seen.

The icterus index is high, depending upon course, amount of hemolysis at the moment, with its consequent increase of bilirubin in the blood. The Van den Bergh test is positive in the indirect phase. There is an increase in urobilin in stools and urine.

Not all cases show an increased fragility of the red cells. Hemolysis begins sometimes in solutions of saline as high as 0.86 per cent and

complete hemolysis occurs at a point where ordinarily most of the corpuscles would not have hemolyzed.

The treatment is splenectomy. This is followed by a rise in the red-cell count and hemoglobin and an increase in the size of the red cells. The number of reticulated cells becomes normal and the resistance of the red cells becomes normal. There is a postoperative leukocytosis which may persist for months. Eosinophils and myelocytes may be found. The icterus disappears after a week or so.

It is difficult to say whether this apparent clinical cure is permanent.

The acquired type pursues about the same course as the familial. (By the acquired type, we do not mean those cases of hemolytic icterus for which there is a definite etiology—as lues, malaria, or certain chemicals.)

The only differences between the congenital and acquired types are that there is no microcytosis in the acquired type, but the anemia is likely to be more severe and in this type they do not transmit this disease.

Thrombopenic Purpura (Werlhoff's Disease, Thrombocytopenia, Purpura Hæmorrhagica).—This condition is not usually familial and is characterized by hemorrhages into the skin or from the mucous membranes. It may be acute or chronic and there is no known etiology. In some of the cases there is only one attack of bleeding. In other cases there were intervals when there is no sign of the condition present and still other cases where the tendency to bleed on slight provocation is always present and the blood-picture seldom returns completely to normal. The spleen is usually enlarged.

The hemoglobin, red- and white-cell count, depend entirely on the amount and duration of the bleeding. The severest anemia is met with in the chronic cases. The red cells show achromia reticulation and marked variation in size and shape. The color, volume and saturation indices are always low, according to Osgood and Haden. Leukocytosis is common but there may be a leukopenia. The differential count is not characteristic.

The platelet-count varies from time to time, but is always low, usually from 50,000 to 100,000. A few cases are reported where the count was in the hundreds. Giant platelets are commonly seen.

The bleeding time is prolonged; instead of the usual three to four

minutes, bleeding times of from eight minutes to twenty-four hours or longer have been reported. Coagulation time is normal.

The tourniquet test (capillary resistance) is always positive in the active stages, and frequently this can be seen when there is no other evidence of the disease.

The clot is non-retractile, soft and friable and very often coagulation is incomplete.

Effect of Splenectomy on Laboratory Findings.—Griffin and Halloway analyzed 28 cases after splenectomy. They found that the number of platelets rose rapidly to above normal, in 3 instances to more than 1,000,000. In 2 cases they remained below 50,000. The tourniquet test became negative soon after the petechiæ and ecchymoses disappeared. They found a great variability in the promptness with which the bleeding time became normal. In 3 cases it was normal within a few hours. In most of the cases it was reduced to less than eight minutes quite promptly and in from five to eighteen days to less than three minutes. They also found a great variability in connection with the recovery of the retractability of the clot. A few of the patients remained somewhat anemic.

The theories regarding the origin of this disease can only be indicated here. Kasnelson believes that the reticulo-endothelial system, especially the spleen which normally plays an important part in the destruction of blood-platelets, becomes overactive and destroys the platelets as fast as they can be produced. The basis for this view is the rise in the number of the platelets after splenectomy which is due to removal of the platelet-destroying organ. A large number of platelets are always found in the spleen. Splenic enlargement is quite common, which might be regarded as due to hyperfunction. Another fact is the excessive number of megakaryocytes in the bone-marrow which can be interpreted as a compensation.

On the other hand, Frank believes that there is a defect in the production of the platelets. Splenectomy does not always cause a rise in platelets and the usual rise is not always permanent.

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CHAPTER III

SEROLOGY

Importance.—Laboratory examinations produce evidence of great value suggesting or leading to the diagnosis of syphilis and the management of the treatment of syphilitic infants and children. The most important and most widely used laboratory methods in infantile and juvenile syphilis are serological and roentgenological examinations. As in adults, single laboratory examinations are not adequate in themselves nor final in the diagnosis of syphilis. The diagnosis of syphilis rests in all the evidence which can be obtained by both complete clinical and laboratory investigation, and the diagnosis is established or determined after the evaluation of the total findings (many of them often repeated several times) rather than the acceptance of the result of a single laboratory examination. In other words, the laboratory findings indicate that certain reactions are positive or negative but are not infallible tests for presence or absence of *Spirochæta pallida* in the patient. The intelligent interpretation of serological reactions is directly dependent on a thorough knowledge of the patient himself. Important characteristics of the patient which are of great significance in evaluating the serological results are (1) age of the patient, (2) age of syphilitic infection in the patient, (3) amount of treatment patient has received (or in early infancy amount of treatment the mother had received during the pregnancy). One must consider all of these elements before venturing an interpretation of the serological results.

The age of the patient is perhaps of greatest importance in early life. In general, during the first four months, the younger the patient, the less reliable are the serological findings. The results of the serological tests on blood from the umbilical cord are particularly prone to error, and one should give a guarded opinion on them in the event of either positive or negative findings. When syphilis is suspected in a newly born infant and there are no clinical signs of the disease, greater reliance should be placed on routine tests taken a week or ten days after birth and every four weeks thereafter to the age of six

months. The interval can then be lengthened to three months until the infant is two years old, after which time semiannual and later annual examination should be made for an indefinite period. Since the widespread treatment of syphilitic women during pregnancy, a large number of infants are seen who have no physical signs of the disease and are under suspicion only because of the known lues in the mother who has been treated during pregnancy. Two most valuable examinations at the time of delivery which should be taken advantage of more frequently are the microscopic examination of the placenta for syphilitic changes and roentgenological examination of bones for syphilitic lesions. If these findings confirm the serological result, the diagnosis is almost certain; if these findings are in conflict with the serological result, each case must be judged individually.

Reliability.—Infants who present clinical manifestations of syphilis are practically always positive serologically. Sensitivity of the Wassermann and the Kahn reactions approaches 100 per cent in such cases even in the first week of life. Occasionally, however, authentic reports have been made of infants with active clinical syphilis and a negative blood reaction which subsequently became positive during treatment. During five years of active service, I have observed one such case. The presence of a negative serological reaction in a case of frank clinical syphilis in no way contra-indicates the immediate institution of treatment.

After the first year of life sensitivity of serological reactions in prenatal syphilis becomes progressively less. Throughout the first decade serological tests are highly sensitive (sensitiveness approximates 90 per cent). With each succeeding decade serological sensitiveness is reduced, second decade 60 per cent, third decade 50 per cent, and in the fourth and fifth decades of life less than half the patients with clinical signs of congenital syphilis have positive serology.

The serological investigation of congenital syphilis should include all available members of the family. This is particularly valuable when the different results and methods of examination are in conflict. The maternal serology is of particular interest in this regard. The paternal serology is also important, but is not so reliable as that of the mother as a confirmatory finding for the child. That is, neither syphilitic infection nor serological results parallel each other in infant and father as

closely as in infant and mother. Fortunately the mother is usually available in clinic practice.

Interpretation.—In the interpretation of serological results one must always be sure of the nature and sensitivity of the test used. Since the introduction of the Wassermann reaction, many changes and modifications have been made at various times which apparently vary widely in both sensitivity and specificity. There is great need for a national, or better an international, standardization of Wassermann reactions. Because of the complexity and indirect *modus operandi,* it is doubtful whether complement fixation tests can be standardized. This fact more than any other has led to the recent developments in standardization and popularization of the precipitation reactions of which Kahn's test has proved very valuable to date. The practical results in several hundred thousand cases and the report of the League of Nations' serological meeting at Copenhagen, in 1928, indicate that the test is equal if not superior to any of the serological reactions in the diagnosis of syphilis. My own experience in comparing Kahn's test with the Noguchi-Wassermann test in infants and children suggests that Kahn's test is slightly the more reliable of the two. It is just as logical in view of the experience to date to use the Kahn test alone as it is to use the Wassermann test alone. However, the use of both tests simultaneously gives more information than either alone, and they serve as excellent checks on each other. We now have two highly specific and highly sensitive serological tests for syphilis. The diagnosis of syphilis is important enough and difficult enough to demand both tests simultaneously on identical sera, particularly in patients who present clinical findings which are not conclusive in themselves.

The serological examination of the spinal fluid is an investigation without which the syphilitic patient cannot be adequately judged nor treatment properly advised. Here again the results must be evaluated in their relation to the other findings. Involvement of the central nervous system in congenital syphilis has been estimated to occur in from 10 to 75 per cent of all cases. The cellular and chemical changes in syphilis of the central nervous system are dealt with in the chapter on spinal fluid examination. The serological reaction in the spinal fluid is of special importance when the decision as to continuance and cessation of treatment must be made. Serological reaction of the spinal fluid may

be positive in cases with negative blood serology, and the reverse is frequently the case. Knowledge of the serological status of the spinal fluid is of considerable importance in estimating prognosis. Serological evidence of syphilitic involvement of the nervous system generally should make one cautious in giving a prognosis.

The presence of weakly positive serological reactions which are confirmed by repeated examinations are often difficult of interpretation. Each case must be judged individually. If the weakly positive serological result is wholly unsupported by other evidence of familial syphilis, the patient should be kept under observation for follow-up examinations, but generally treatment under such conditions is not justifiable. The presence of strongly positive serological results which can be repeatedly confirmed generally indicates treatment, even though no collateral evidence of syphilis can be established. In such cases lighter schedules of therapy should be emphasized if the patient is in good general condition and responds well to the antisyphilitic preparations used.

Relation to Treatment.—The so-called "Wassermann-fast" cases present considerable difficulty in management of their treatment. After years of vigorous treatment, some patients show repeatedly four-plus reactions, even though their general health and development are satisfactory. Some have taken the stand that these cases should be treated intensively as long as the serology is positive. Others, notably Wile, have advised lighter schedules of treatment for such cases. In general, I believe such cases are usually overtreated, and although they should be kept under observation and examined at intervals, longer rest periods should be allotted to them, as well as shorter periods of treatment. Quantitative studies of these so-called "fast" cases by precipitation will probably reveal much of value. In the few cases studied to date, our results indicate that, although these reactions may be four plus, from a quantitative standpoint they are not strongly positive reactions. Chesney's suggestion that the spirochetal activity in man might be investigated by examination of lymphatic glands and animal inoculation seems particularly appropriate in serologically "fast" cases. Positive results by such investigation would indicate viable spirochetes in the lymphatics of such patients, which would argue for continued treatment.

CHAPTER IV

FECES

No attempt will be made here to go thoroughly into the microscopic, macroscopic, chemical and bacteriological examination of the stools of infants and children. We will take up those conditions where a stool examination is of some use in diagnosis, and discuss the interpretation of the findings. When one wants accurate information as to parasites, bacteria, and chemistry of the feces, it should be done by those who are thoroughly trained and experienced in this kind of work.

STOOLS IN THE NEWBORN

The meconium stools excreted in the first days of life are blue-black, tenacious, homogeneous and without odor. These are followed by dark-brown, then yellow-brown, excretions which still have the consistence of meconium. Normally, meconium is bacteria-free and little or no putrefaction goes on. It usually contains blood pigments. On the third to fifth day the stools become like those of the lactation period, and by the seventh day they are yellow and have the characteristic sour smell.

STOOLS IN INFANCY

The number, size, and character of the stools vary with the age, food, and the state of the intestinal tract as to fat, protein, and carbohydrate digestion. Breast-fed babies have more frequent movements than bottle-fed babies. The stool of the breast-fed infant is larger, more moist, acid, light yellow rather than yellow-brown, and aromatic instead of foul as compared to the stool of the bottle-fed baby.

Acidity.—Within recent years several studies have been made on the P^H of the stools of infants. In a recent careful study Tisdall and Brown found that the P^H of the stool of the normal newborn breast-fed infant was singularly constant, varying between 4.7 and P^H 5.1. In artificially fed infants the P^H varied widely (from P^H 4.6 to P^H 8.3). The more acid stools were encountered only in infants with severe

diarrhea. With acid milk the stools were usually more alkaline than P^H 7.0. The acidity of the stools was usually increased in the presence of parenteral infections. Strongly alkaline stools were obtained by feeding whole lactic milk to which large amounts of sugars had been added. No difference was noted in the action of Karo, dextrimaltose or cane sugar. Tisdall and Brown believe that acidity of the stool depends on the ratio "in the zone of fermentation" of the carbohydrate, the protein and base.

Abnormal Stools in Infancy.—Too much emphasis should not be placed on stool reports. The stool examination may indicate certain definite conditions, but it should always be interpreted in conjunction with the feeding history and physical examination.

Curds.—Curds in the stool indicate incomplete digestion or a too rapid passage through the tract. The large white casein curds point to imperfect digestion of raw cow's milk. Yellow fat curds are the result of incomplete digestion or absorption of fat. The presence of fat and protein curds does not necessarily mean fat and protein indigestion. They are one symptom of something wrong.

Mucus.—A small amount of mucus is present in normal stools. When present in excess it means intestinal irritation. It is often found in large masses, occasionally as a cast of the bowel. It is always found after castor oil.

Starvation Stool.—The starvation stool is small, loose, dark green, and is composed of bile, mucus, intestinal secretions and bacteria. The odor is stale and musty.

Fat Indigestion.—In fat indigestion the stools may be loose or constipated. If neutral fat predominates, the consistency is creamy; if soaps predominate, it is crumbly. The reaction is acid, the odor rancid, and the color light yellow. The fat content may reach as high as 60 per cent as compared to a normal of 10 to 20 per cent. The bacterial smear shows a predominance of Gram-positive organisms.

Protein Indigestion.—In protein indigestion the stools may be loose or constipated. They are usually alkaline with a foul odor and are dark in color. Gram-negative organisms predominate, and the fermentation test shows protein fermentation.

Carbohydrate Indigestion.—In carbohydrate indigestion the stools are loose, frothy, yellow or green, strongly acid in reaction, and Gram-

positive organisms predominate. The fermentation test shows carbohydrate fermentation.

Chronic Intestinal Indigestion.—In chronic intestinal indigestion (celiac disease) the stools alternate between constipation and diarrhea. They are always large, the color is light gray or white, and the odor is quite foul. With diarrhea they are large, green or brown, acid, sometimes frothy, and contain undigested food and large amounts of mucus. Large amounts of fat, as high as 60 to 70 per cent, are found. Carbohydrate fermentation is marked, and Gram-positive organisms predominate.

Hirschsprung's Disease.—In Hirschsprung's disease (megacolon), which has to be differentiated from celiac disease, the stools are quite different. During periods of constipation they are at times dry and inspissated or of puttylike consistence, yellowish-green in color, and of foul odor. Diarrhea may be present with ulceration of the gut, and the stools then show blood and mucus.

Chronic Constipation.—In chronic constipation the stools are small, dry, compact, and hard, but are otherwise normal unless associated with some digestive disease.

Intestinal Intoxication.—In intestinal intoxication (acute intestinal indigestion) the stools are increased in number and are at first fecal in character. Later they become watery and green, and contain undigested food and mucus. They may have a sour or foul odor depending on the food that has been ingested. Blood is not usually present. Holt, Courtney and Fales showed "the average composition of diarrheal stools to be about 93 per cent water and 7 per cent solids. Normal stools showed 80 per cent water and 20 per cent solids. The relative amounts of fat, protein and ash in diarrheal stools is nearly the same as in normal stools; but the form in which they exist differs notably. In diarrheal stools nearly two-thirds of the fat is in the form of neutral fat, and only one-twelfth in the form of soaps. In normal stools only one-third is neutral fat, while more than half exists as soaps. There is great difference also in the composition of the ash. In normal stools sodium, potassium, and chlorin together make up but 11.2 per cent of the ash; in diarrheal stools they form 48.7 per cent of the total. There is, then, in diarrhea a great draining away from the tissues of both water and soluble salts, particularly sodium chlorid."

Dysentery.—At first the stools in this condition are frequent and watery. Later they contain blood and mucus and shreds of pseudo-membrane which can with care be distinguished from mucus. The stools increase in frequency, though the amount may be small, occasionally watery, but blood, mucus and pus are passed. There is not much odor.

Intestinal Tuberculosis.—Diarrhea is common and the stools differ very little from those seen in dysentery except that tubercle bacilli are found and hemorrhages are frequent.

Intussusception.—Diarrhea is not common, but bloody stools are the rule. Very little feces is passed, and with the blood there may be mucus.

Catarrhal Jaundice.—Rarely the stool may contain bile, but usually it is a gray or white color.

Hemolytic Jaundice.—The stools are somewhat darker than normal and most workers find a marked increase in urobilin in the stool in this type of anemia. In other types of anemia with blood destruction consistent results are not found in children.

Blood may be found in the stools in the following conditions:

Ulcers (tuberculous and typhoid)
Dysentery
Enterocolitis
Intestinal parasites
Hemorrhoids
Prolapse of rectum
Acute infections
Purpura
Trauma
Swallowing of blood from nose and throat
Cirrhosis of the liver

BACTERIOLOGY OF THE FECES

The identification of the various organisms of the intestinal tract is exceedingly difficult and requires the skill of a trained bacteriologist. It is possible now to separate the members of the typhoid, colon and dysentery groups.

A great deal of work is being done on other bacteria in the stool (streptococci associated with arthritis, etc.) in the attempt to incrimi-

nate the intestinal tract as a focus of infection. This work has not reached the stage where definite statements can be made.

Many attempts have been made to connect certain types of fecal flora with certain clinical conditions in infancy and childhood. Most workers are agreed that the so-called "fermentation" and "putrefactive" types of stool flora occur frequently in normal children and are without significance.

Tubercle bacilli in the stool do not necessarily mean intestinal tuberculosis. In young children sputum is almost always swallowed. With blood and mucus in the stool and other signs of ulceration of the gut present, the finding of tubercle bacilli would point to intestinal tuberculosis.

Bacteriology of the feces is important in the diagnosis of typhoid fever, and typhoid carriers, and the various types of dysentery. For methods of detecting these organisms, the reader is referred to various works on bacteriology.

CHEMISTRY OF THE FECES

It is doubtful if the man in practice will get much information from a chemical examination of casual specimens of stool. Fat determinations in a case of celiac disease are of interest in diagnosis and following the course of this condition. In other conditions the clinical value of chemical examinations is questionable. The following summary of the chemical composition of the stool is taken from Holt and Howland:

The only gases usually present are hydrogen and carbon dioxid. Sulphurated hydrogen and marsh gas, to which the odor of adult stools is largely due, are not present.

The solids of the stools are chiefly fat, salts and nitrogenous material. Sugar is not found, but its derivative, lactic acid, may be present in small amount. The fat forms nearly 40 per cent of the dried matter of the normal stool of the nursing infant; nearly 50 per cent of this fat is in the form of soaps; 35 per cent, free fatty acids; 15 per cent, neutral fat. In the normal stools of infants fed upon cow's milk about 35 per cent of the dried matter is fat, of which nearly three-fourths is in the form of soaps. The inorganic salts form about 10 per cent of the dried matter of the normal stool of the nursing infant, and from 20 to 30 per cent of that of the infant taking cow's milk; in both more

than four-fifths of the total is calcium phosphate. The nitrogenous elements of the cow's milk stool form about 25 per cent of the dried matter, but only a small part of this represents unabsorbed protein. The chief source is intestinal secretions and the bodies of bacteria. Amino-acids, representing unabsorbed food protein, form from 2.4 to 24 per cent of the nitrogen of the stool. The protein of woman's milk is almost all absorbed.

A healthy nursing infant absorbs from 90 to 98 per cent of the fat taken, from 85 to 95 per cent of the protein, and from 80 to 85 per cent of the salts. A healthy infant taking cow's milk absorbs about 85 to 90 per cent of his ingested fat, about 90 to 95 per cent of his protein, and about 60 per cent of his salts.

The biliary elements present in the stool are urobilinogen, urobilin, and cholesterin. The presence of biliary acids is doubtful. Mucus is always present in considerable quantity.

If the infant is taking a food containing starch, this may appear to a greater or less extent in the stools, a larger amount in the case of very young infants.

INTESTINAL PARASITES

Of the many intestinal parasites, those of chief practical importance, because of their pathogenicity in infants and children, are found among the protozoa and vermes, or worms.

The protozoa most frequently encountered in general practice are *Entamœba histolytica, Lamblia intestinalis* and *Balantidium coli.* The worms met with belong to the orders of Nematodes and Cestodes. The Nematodes are represented by the *Oxyuris vermicularis, Ascaris lumbricoides, Trichocephalus dispar* and *Ankylostoma duodenale;* the Cestodes by *Tœnia saginata, Tœnia solium, Tœnia nana* and *Bothriocephalus latus.*

The reader is referred to Volume VIII of this series for the clinical features of infestation by these parasites. We are here concerned chiefly with their morphology and identification.

Entamœba Histolytica.—This rhizopode of the class Sarcodina is the etiologic factor in amebic dysentery and is frequently referred to as the *Entamœba dysenteriæ.* The active forms measure from 20 to 30 micra and are practically colorless except for a finely granular endo-

plasm. The nucleus, which varies from 4 to 7 micra in diameter, is visible only under favorable conditions during life, but a deeply staining central mass, the karyosome, identifies it in the prepared specimen (Fig. 3).

Staining Methods for Amebæ.—Simon recommends staining the fresh specimen with dilute neutral red. A drop of dilute aqueous solution of the stain is allowed to run under the cover-glass, or a

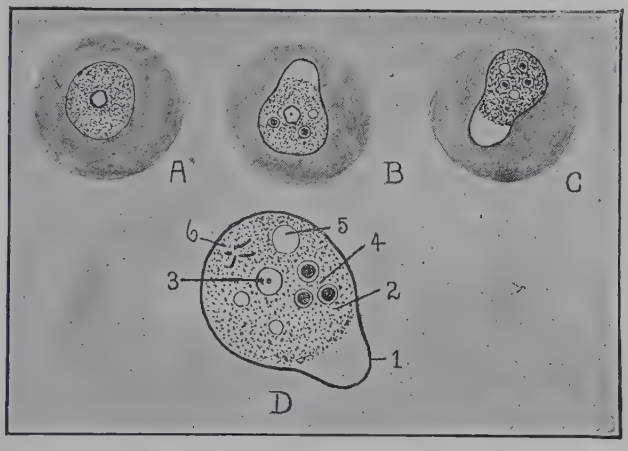


Fig. 3.—Parasitic Amebæ.

A, *Entamœba coli;* B, C, *Entamœba dysenteriæ;* D, diagrammatic: 1, ectoplasm; 2, endoplasm; 3, nucleus, nuclear membrane, centriole; 4, erythrocytes; 5, vacuole. (Adapted from Craig.)

minute particle of the powdered stain may be added to the specimen. There is a selective staining of the endoplasm of the parasite. Ameboid movements seem not to be interfered with. The organisms stand out very prominently.

Stained Preparations.—It is difficult to obtain satisfactory stained specimens of amebæ. They may be stained with hematoxylin or with one of the Romanowsky stains. Brem has had excellent results with a technic of his own. Cover-slip preparations are made from the bloody mucus, and the specimens are then stained with Wright's, Hastings's, Leishman's, or Wilson's stain in the following manner:

1. The unfixed specimen is covered with four drops of the stain, which is allowed to act for ten to fifteen seconds. Since the stain is dissolved in absolute methyl alcohol, this fixes the specimen.

2. Add to the stain four drops of distilled water. At the end of one minute—

3. Add four more drops of stain. Again, at the expiration of one minute—

4. Add four drops of water. The specimen is thus covered with a mixture of stain and water in equal quantities. This is permitted to act for ten to thirty minutes.

5. The specimen is now washed in distilled water. (The cover-glass should be kept level, while a stream of water is directed against its surface. In this way, the precipitated stain is washed or floated off; dumping the staining mixture from the specimen causes the precipitate to adhere to it.) The specimen is quickly dried by holding it over a small flame or preferably by blotting it carefully, and is mounted in balsam.

The ectosarc of the amebæ is stained dark blue, the endosarc a light blue. The nucleus takes a brilliant purplish-red color, and bacteria contained in the endosarc have a somewhat similar color. Phagocyted erythrocytes show a pinkish tint.

Lamblia Intestinalis.—This flagellate of the class Mastigophora, although not sufficiently pathogenic to regularly produce characteristic disease, may cause functional disturbances in certain individuals. Giardia infection (from the synonym *Giardia lamblia*) is quite common in children. Maxcy finding it in 20 per cent. Transmission is accomplished through contamination of food or water with material containing the cysts.

Fig. 4.—Giardia Intestinalis.

Ventral and lateral views, with dead parasite between; upper right, parasites on the intestinal epithelial cells; lower right, encysted parasite. (After Grassi and Schewiakoff, from Braun.)

Viewed ventrally or dorsally, the parasite is pear-shaped, measuring from 9 to 20 micra in length by 5 to 10 micra in width, and having

a cuplike sucking-disk situated anteriorly on its ventral surface. It is provided with eight flagella arranged in pairs. The nucleus may be seen at times beneath the depression. The encysted form is egg-shaped and very transparent, showing the lamblia within (Fig. 4). Purgatives will frequently bring down these parasites.

Balantidium Coli.—Producing a disease somewhat similar to amebic dysentery, this ciliate of the class Infusoria was first described by Malmsten, in 1857. The parasite is oval, varying in size from 30 to 200 micra or more in length, by 20 to 70 micra in breadth. The surface of the body is covered with cilia which arise from parallel longitudinal lines that give the body a striated appearance. Two or more vacuoles are found in the endosarc, and a macronucleus, rather kidney-shaped, and a round micronucleus, situated posteriorly, may be seen (Fig. 5).

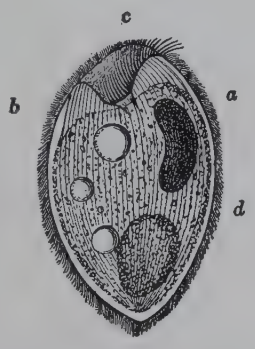


FIG. 5.—BALANTIDIUM COLI.

A, nucleus; B, vacuole; C, perostome; D, food mass. (After Leuckart, from Braun.)

Oxyuris Vermicularis.—The common pin-worm or seat-worm is a small nematode, the males measuring 3 to 5 millimeters in length with the posterior end curved, the females being about 10 millimeters long and 0.6 millimeter thick. The ova (Fig. 6) are flattened on one side, measure 0.016 to 0.025 by 0.050 to 0.055 millimeter, and have a clear, thin shell.

Ascaris Lumbricoides.—The ordinary round-worm of man is the largest of the commoner parasitic nematodes. It is found in the feces or vomitus while its ova occur in the stool. The males average about 20 centimeters in length by about 3 millimeters in thickness, the females being on an average about half again as big. The ova are elliptical (Fig. 7, 1 and 2) and have a thick transparent shell, which at times appears laminated. They measure about 0.045 by 0.06 millimeter. The living worm has a reddish or grayish-yellow color.

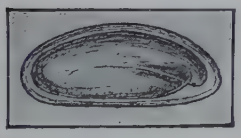
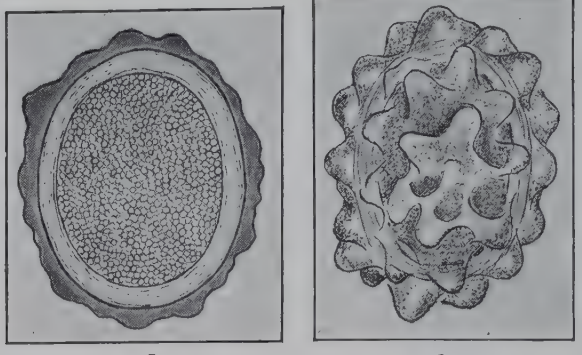


FIG. 6.—OVUM OF OXYURIS VERMICULARIS. (× 460.)

Trichocephalus Dispar.—The whip-worm or thread-worm, also known as *Trichuris trichiura,* is rarely seen in the feces, although it may be found after treatment has been administered. The males are

34 to 45 millimeters long, the females 35 to 55 millimeters. The eggs are oval in shape (Fig. 8) with a relatively thick shell, which is generally stained dark yellowish-brown. The ova are 0.05 millimeter long and 0.024 millimeter wide.

Ankylostoma Duodenale.—The Old World hookworm is of frequent occurrence in this country, often associated with *Necator americanus,* being very prevalent in the Southern States. The two varieties are essentially similar, the ova being identical in appearance (Fig. 9). The adult worms of *Necator americanus* are found in the stools only after treatment. They are small, whitish, grayish, or reddish-brown in color, and have the anterior end curved dorsally to form a hook (Fig. 10). The males measure 6 to 10 millimeters in length, the females 8 to 15 millimeters. The adult *Ankylostoma duodenale* is slightly larger than the American variety.



1 2

Fig. 7.—(1) Ovum of Ascaris Lumbricoides; (2) The Same under High Focus Showing the Albuminous Coating. (× 460.)

Tænia Saginata.—The beef tapeworm is a cestode which measures 4 to 10, even 36 millimeters in length when fully developed. From the hermaphroditic segments, ova (Fig. 11, 2) are deposited in the feces. These are round or oval, measuring 0.035 by 0.025 millimeter. The shell is rather thick, radially striated and light brown in color. It contains three pairs of hooklets. The mature segment or proglottis (Fig. 11, 1) is 16 to 20 millimeters long and 4 to 7 millimeters broad.

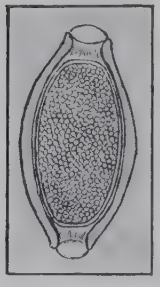


Fig. 8.—Ovum of Trichuris Trichiura. (× 460.)

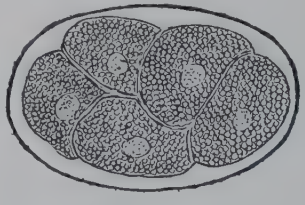


Fig. 9.—Ovum of Necator Americanus. (× 460.)

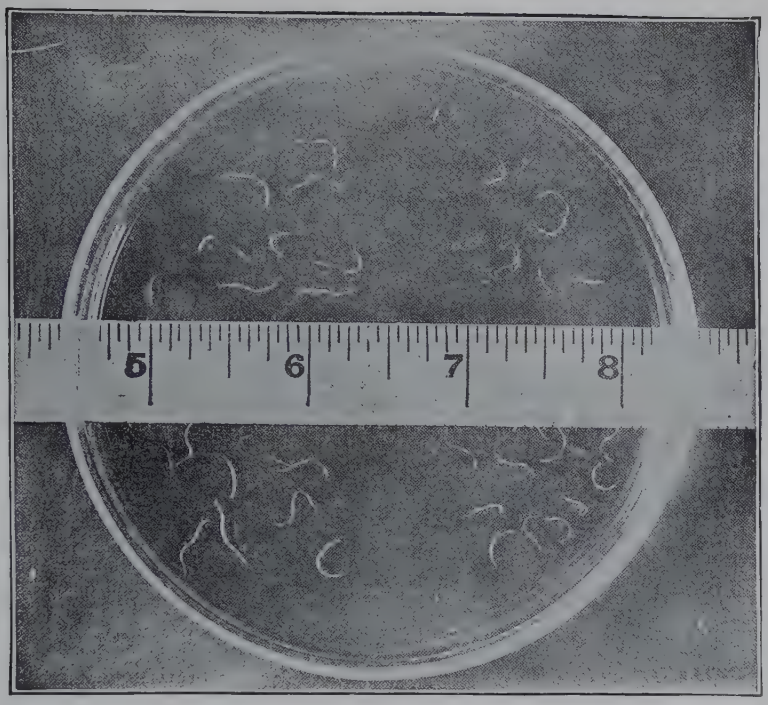


FIG. 10.—NECATOR AMERICANUS.
Upper half males, lower half females. Inch measure (after Dock and Bass).

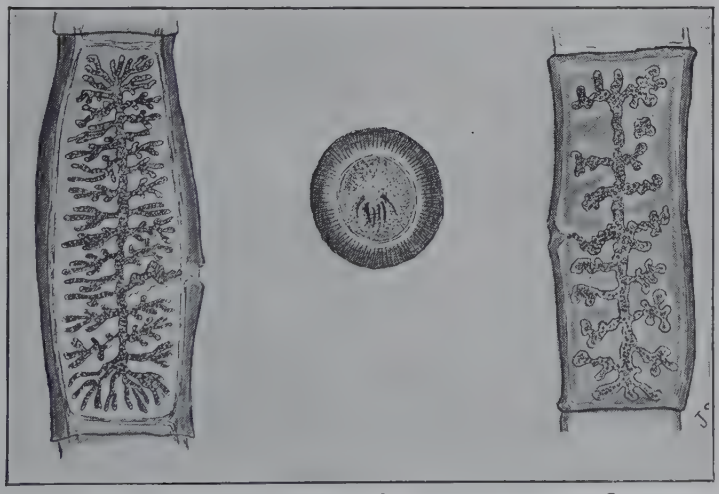


FIG. 11.—(1) GRAVID PROGLOTTIS OF TÆNIA SAGINATA (× 4); (2) OVUM OF TÆNIA SAGINATA (× 460); (3) GRAVID PROGLOTTIS OF TÆNIA SOLIUM (× 4.)

From the ova alone it is impossible to distinguish between *Tænia saginata* and *Tænia solium*. The characteristic difference is found in the branching of the central stem, or uterus, of the mature segments.

FIG. 12.—OVUM OF HYMENOLEPIS NANA. (× 460.)

Tænia Solium.—The pork tapeworm, when mature, measures 2 to 3 millimeters in length, while the ova are about 0.035 millimeter in diameter. The mature segments (Fig. 11, 3), which are often seen in the feces are 10 to 12 millimeters long and 5 to 6 millimeters broad. The uterus has only seven to ten lateral branches extending to either side, and they do not tend to rebranch, as do those of *Tænia saginata.*

Tænia Nana.—The dwarf tapeworm, also known as *Hymenolepis nana,* is a very common parasite in children, but because of its small size, the segments are seldom found in the feces. The fully developed parasite is 10 to 45 millimeters long and from 0.5 to 0.9 millimeter thick. The head is round and presents a simple crown of 24 to 30 hooklets. The ova are spherical or oval (Fig. 12), measuring between 0.036 to 0.056 millimeter long and 0.032 to 0.042 millimeter broad. The oncosphere presents three pairs of hooks, usually directed toward one pole.

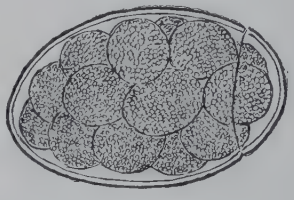


FIG. 13.—OVUM OF DIBOTHRIOCEPHALUS LATUS. (× 460.)

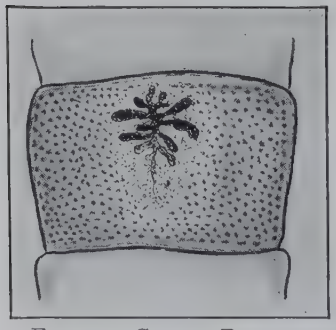


FIG. 14.—GRAVID PROGLOTTIS OF DIBOTHRIOCEPHALUS LATUS. (× 4.)

Bothriocephalus Latus.—The fish tapeworm, also known as *Dibothriocephalus latus,* measures about 9 millimeters in length when mature. The ovum (Fig. 13) has a rather thin, clear, white or brownish shell, with a small operculum or cap which stands out particularly well after treatment with glycerin or dilute sulphuric acid. The eggs are elliptical and measure 0.068 to 0.070 by 0.0044 to 0.045 millimeter. The segments (Fig. 14) may be found in the feces, and differ from the two preceding parasites in that they are broader than they

are long. The dark brown, rosette-shaped uterus, placed near the center of the segment, distinguishes the parasites. There are no hooklets in the ova. The head is 2 to 3 millimeters long and is unarmed.

CHAPTER V

THE SPUTUM

In infants and young children it is difficult to obtain sputum. In looking for tubercle bacilli it is better to examine the stomach contents. To get sputum for pneumococcus typing, the child may be made to cough on a swab. For details of the general and bacteriological examination the reader is referred to appropriate textbooks.

MACROSCOPIC EXAMINATION OF SPUTUM

Characteristic Appearance.—In some conditions the appearance of the sputum is more or less characteristic.

Pneumonia.—Older children may have the same sputum as adults, tenacious and blood-tinged at first, later becoming abundant and yellow. Children under five years rarely expectorate.

Tuberculosis.—There is no characteristic sputum in pulmonary tuberculosis.

Asthma.—In uncomplicated cases the sputum is characteristic. It is clear, white, tenacious, and contains little round masses like tapioca balls in mucus, the "pearls" of Laënnec. Curschmann's spirals, Charcot-Leyden crystals and eosinophils are also found. If infection occurs, the sputum may become yellow-green and purulent.

Whooping-Cough.—There may be no sputum in the early catarrhal stage. In the spasmodic stage it consists of tenacious mucus. The *B. pertussis* is found in the early spasmodic stage.

Abscess of the Lung.—The sputum in this condition has an offensive odor, is purulent, may be blood-tinged and contain yellow elastic tissue. The amount is variable depending on the size of the abscess, and the communication with the bronchi.

Gangrene of the Lung.—Sputum in this condition has a characteristic putrid odor, and may contain pieces of necrotic tissue. It usually separates into three layers, a heavy green or brown sediment, a thin green liquid layer, and a frothy layer on top.

Bronchiectasis.—Large amounts of gray or brown (occasionally blood-tinged) fetid sputum are coughed up once or twice a day. It

separates into three layers, a gray sediment, a fluid middle layer, and a brown froth on the top.

BACTERIOLOGY OF THE SPUTUM

Only a few of the bacteria found in the sputum will be considered here. For details and cultural methods consult works on bacteriology.

Bacillus Tuberculosis.—When sputum can be obtained the organism is looked for in the smear stained in the usual way. In young infants it is easier to examine the fasting stomach contents.

Bacillus Influenzæ.—*Bacillus influenzæ* can be recognized in the stained smear, but should be cultured out for complete identification.

Bacillus Pertussis.—*Bacillus pertussis* is found in pure culture early in the spasmodic stage of the disease. Specially prepared potato blood-media is used and the child made to cough directly on the plate.

Pneumococcus.—The pneumococcus is found frequently in the throats of normal infants and children, and will predominate in the sputum of cases of pneumonia and other acute respiratory infections.

Bacteriology of Pneumonia in Children.—The most recent work in this field is that done by Plummer, Raia, and Schultz. They have studied 154 cases of lobar and bronchopneumonia in infants and children with 156 control cases. They have compared the results with those obtained in adults and have reviewed the literature. Through the kindness of these workers, I am able to give the following summary of their work which is shortly to be published.

Method.—The routine typing was done from throat swabs. The pharynx was streaked several times until the patient coughed. By this method a specimen of thick, tenacious sputum was seen to adhere to the swab. The swab was put in 3 c.c. of beef heart infusion broth P^H 7.8. This was incubated three hours, inoculated into a mouse and streaked on a plate. Blood-cultures were taken and specimens of sputum, ear exudate, or chest fluid were obtained whenever possible. Post-mortem lung punctures were done on many of the fatal cases, and lung tissue obtained at autopsy was cultured. In 34, or 87 per cent, of the 39 cases, the organism obtained by the throat swab and considered to be the cause of the pneumonia was verified by a culture from some other body fluid or exudate.

Cooper, Edwards, and Rosenstein have obtained ten immunological

types from the group IV pneumococci which they have designated IV-XIII. Recently seven additional types have been separated.

The following table summarizes the previous work in children by Wollstein and Benson, Pisek and Pease, Mitchell, Lyon, Wollstein, Webster, and Westlund. It includes data on 614 cases. The adult figures were taken from the series reported by Avery, Chickering, Cole and Dochez, Cecil, Larsen and Baldwin, Park, Bullowa and Rosenbluth, and Cecil and Sutliff.

Pn. I		Pn. II		Pn. III		Pn. Uncl.		No Pn.		Total
No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	
CHILDREN (COMPOSITE OLD CLASSIFICATION)										
99	16.1	61	9.9	26	4.2	326	52.9	105	17.1	614
ADULTS (COMPOSITE OLD CLASSIFICATION)										
1318	32.6	839	20.7	508	12.6	1380	34.1			4045
BELLEVUE SERIES (CHILDREN OLD CLASSIFICATION)										
15	9.7	3	1.9	3	1.9	126	81.8	7	4.5	154

INCIDENCE OF TYPES IN PNEUMONIA, BELLEVUE HOSPITAL
(New Classification)

Type	Adults		Children	
	Cases	Per Cent of Incidence	Cases	Per Cent of Incidence
I	75	18.1	15	9.7
II	140	33.7	3	1.9
III	31	7.5	3	1.9
IV	17	4.1	4	2.6
V	32	7.7	9	5.8
VI	7	1.7	18	11.7
VII	16	3.9	5	3.2
VIII	3	0.7	1	0.7
IX	6	1.4	7	4.6
X, XI, XII, XIII	8	1.9	4	2.6
Unclassified	72	17.3	78	50.7
Miscellaneous	8	1.9	7	4.6
Total	415		154	

This table shows that the unclassified group is reduced from 81.8 per cent to 50.7 per cent by the inclusion of the ten new groups. Type VI is found more frequently than type I and types IV, V, VI, VII, and IX occur more often than either type II or III. Type VI is much more prevalent in children than in adults.

The following table shows the type incidence in lobar and broncho-pneumonia.

Type	Total Number of Cases	Lobar Pneumonia	Broncho-pneumonia
I	15	14	1
II	3	3	0
III	3	0	3
IV	4	4	0
V	9	9	0
VI	18	10	8
VII	5	4	1
VIII	1	1	0
IX	7	6	1
X, XI, XII, XIII	4	2	2
Unclassified	78	61	17
Miscellaneous	7	5	2
Total	154	119	35

Certain types seem to predominate in lobar and other types in broncho-pneumonia, but the series is too small to make definite conclusions.

There are not enough cases to give definite information in regard to the severity of the various types. The mortality for the series was 17.5 per cent. In type I pneumonia the rate was low—6.6 per cent (adult rate 30.6 per cent) but 11 of the 15 cases were in the 3- to 12-year group. The death rate in the type VI and unclassified pneumococcus pneumonia, which cases are very evenly distributed throughout the different age groups, is very nearly the same as in the complete series.

Complications.—Empyema occurred in 14 cases (all lobar pneumonia) of which 10 were in the fixed types, and 4 in the unclassified group. Three of 78 cases of unclassified pneumonia developed empyema, while 6 of 15 cases of type I pneumonia had this complication. All 6 of these recovered.

Bacteriemia.—Blood-cultures were taken whenever the condition of the patient was serious enough to suggest the possibility of a positive

blood-culture. In 6 of 103 cases a bacteriemia was discovered. Types IV, V and VII were found in the 3 that died and those that recovered were in the unclassified group. Cecil states that one-third of all cases of lobar pneumonia show a positive blood-culture.

Acute nephritis occurred in 4 of the 154 cases, once in type V and the other times in the unclassified group.

Otitis media occurred in 25 cases, 20 of which were in the fixed types and 3 in the unclassified types.

CHAPTER VI

GASTRIC CONTENTS, ORAL AND NASAL SECRETIONS, TRANSUDATES AND EXUDATES, GONORRHEA

GASTRIC CONTENTS

It is not thought that the examination of gastric contents in infants and children has any clinical value as yet. What follows is a brief summary of the information available in this field.

Various methods have been used to determine the degree of gastric acidity. The acid may, by the use of various special indicators, be titrated into fractions and the results expressed in terms of total hydrochloric acid, combined hydrochloric acid, and free hydrochloric acid. This method has been widely used in adults and has yielded results of considerable value.

A second method is the determination of the concentration of hydrogen ions. This procedure gives results of greater significance since acids are dependent for their characteristic properties on the free hydrogen ions. This has been the method of choice in infants. It is customary to express results of hydrogen-ion determinations in terms of P^H, that is, as negative exponents of the logarithms of the true hydrogen-ion concentration.

The hydrogen-ion concentration of the gastric contents in infants varies widely depending on several factors, among which may be mentioned the age of the child, the time of withdrawing the specimen, admixture with saliva, psychic disturbances and variations in body temperature. Of the utmost importance is the type of food given. Following the ingestion of human milk, the average P^H of the gastric contents is about 3.8. Cow's milk contains large amounts of buffer salts which bind the gastric acid and hence the P^H following cow's milk ingestion is considerably higher than after human milk. In a group of infants unaccustomed to cow's milk, Marriott found the average gastric acidity to be P^H 5.3. In another group who had been fed cow's milk for a considerable length of time the gastric acidity

averaged 4.75. This makes it seem likely that infants are able to adapt themselves to the cow's milk to some extent but the P^H still remains considerably higher than after human milk. When milk soured either through bacterial fermentation or by the addition of lactic acid is given, the gastric acidity at the height of digestion approximates very closely that found after the ingestion of human milk (average 3.71). A similar favorable action on the gastric acidity is probably attained after the addition of hydrochloric or other acids to the cow's milk.

The degree of gastric acidity is of importance in relation to activity of the gastric enzymes. Rennin is active at about P^H 6.0. Gastric lipase is 50 per cent active at P^H 6.0 and reaches full activity at P^H 4.5 to 4.0. Pepsin requires a much higher acidity. It begins to act at P^H 5.0, reaches 50 per cent activity at P^H 4.0 and full activity at P^H 2.3, a point probably never attained in the infant's stomach. The observations mentioned above show that even after the ingestion of human milk or acid milk, pepsin at the height of digestion is only slightly more than half active. It should be remembered that by the time a gastric acidity favorable to peptic activity has been reached, a considerable proportion of the ingested food has left the stomach. After whole cow's milk feedings, even in infants who are accustomed to this food, the pepsin activity is either very slight or entirely absent. It is by no means clear to what degree peptic digestion is important in infants.

Another function attributed to the gastric acidity is its antiseptic action. At P^H 5.0 there is marked inhibition of the growth of members of the colon, dysentery and typhoid group of bacilli and at P^H 4.0 there is complete inhibition or death. Bacterial invasion of the duodenum may be a contributory factor in the production of diarrhea in infants.

A number of other functions have been ascribed to the gastric acidity. Of interest among these is the possible relationship between the absorption of calcium from the gastro-intestinal tract and the P^H of the gastric contents. Scheer has found that infantile tetany, a condition in which the serum calcium is markedly reduced, may be cured by the oral administration of HCl. It is also known that calcium chlorid which is curative in tetany acts in the stomach as does hydrochloric acid, and Gamble has calculated that 1 gram of calcium chlorid is equivalent in action to 75 c.c. of decinormal hydrochloric acid. A

decrease in the gastric acidity has been noted during fever and in infants with tetany. Babbott and his coworkers offer the suggestion that the hypocalcemia in tetanic infants is due to the increased P^H of the gastric contents. This in turn is dependent on the numerous febrile affections to which infants are subject during the winter months. They found that, accompanying a rise in serum calcium resulting from ultraviolet ray treatment, the gastric P^H falls.

Hydrogen-Ion Concentration of Duodenal Contents in Infants.—Davison has studied the hydrogen-ion concentration of the duodenal contents. He found that, generally speaking, the enzymatic activity of the duodenal contents was greater in the alkaline than in the acid specimens. There is a direct relationship between the acidity of the gastric and duodenal contents, the more acid the gastric contents the higher was the acidity of the duodenal contents.

The hydrogen-ion concentration of the duodenal contents is practically always acid. On whole milk the P^H varies from 5.0 to 6.5. On some form of lactic acid milk the values vary from 3.3 to 7.7. Davison feels that the reaction of the diet has no influence on the reaction of the duodenal contents.

The acidity apparently has no effect on sterilizing the duodenal contents. Davison found that an equal number of acid and alkaline specimens were sterile.

ORAL AND NASAL SECRETIONS

Diphtheria, Vincent's angina and thrush are common conditions of the nose, mouth and throat, where the laboratory can aid in diagnosis.

Diphtheria.—Cultures should be taken in order to confirm a clinical diagnosis of diphtheria or to detect carriers. One should never depend on a laboratory diagnosis of diphtheria. The clinical diagnosis is more accurate. Direct smears are worthless in diagnosing diphtheria.

If the culture shows organisms which have the morphological characteristics of *B. diphtheriæ,* it usually means that *B. diphtheriæ* is present. It does not always mean that the patient has diphtheria. The organisms may be diphtheroid bacilli or they may be virulent or avirulent diphtheria bacilli from a carrier. If acute inflammation of the throat is present, it should be treated as diphtheria. We wish to emphasize again that antitoxin should be given on the basis of a

clinical diagnosis without waiting for a report on the culture. When diphtheria bacilli are found in an apparently healthy child, or when they persist after recovery from diphtheria, the virulence test should be done.

Membranous Inflammation.—Membranous inflammation is often present with other organisms and without *B. diphtheriæ*. Streptococcus, staphylococcus, pneumococcus can also cause an inflammation which cannot be distinguished from diphtheria.

Vincent's Angina.—There is much confusion regarding the identity of the organisms in this disease. Whether it is a single organism showing pleomorphism or two organisms growing in symbiosis is not settled. At any rate there are two forms, a slender spiral with pointed ends showing five to eight undulations. The fusiform bacilli are 6 to 12 micra long with rounded cells and somewhat thicker in the middle. They are sometimes curved, and sometimes S forms are seen. They stain well with dilute carbolfuchsin or Wright's stain. They can be cultivated anaërobically.

These organisms are sometimes found in healthy mouths.

The pseudomembrane, usually on a mucous surface, may be confused with diphtheria or tonsillitis. An examination of the direct smear will make the diagnosis.

Oïdium Albicans.—Oïdium albicans is thought to be the fungus that forms white patches on the tongue and mucous membrane of the mouth. When examined microscopically the membrane is found to consist of a branching fungus, segmented, and with sporelike bulbs at the ends. Epithelial cells and white cells are scattered in the meshes of the fungus.

EXUDATES AND TRANSUDATES

The examination and interpretation of findings in fluids obtained by puncture (pleural, peritoneal, pericardial) is the same as in the adult.

It is important to differentiate between an inflammatory exudate and a non-inflammatory transudate. The following points will be helpful: In an exudate the specific gravity is usually high—1.018 or higher—the protein ranges from 3 to 7 per cent, and lymphocytes or pus-cells usually predominate. Bacteria can be demonstrated by smear, culture or animal inoculation. In a transudate the specific gravity is lower than 1.015, the protein content is less than 3 per cent, endothelial

cells and lymphocytes are found, but no pus-cells, and the fluid is sterile. Red cells are not present unless due to trauma of puncture.

Tubercle bacilli may be demonstrated best by animal inoculations. Other organisms, pneumococcus, streptococcus, etc., can be cultivated by ordinary means.

GONORRHEA

The most common gonococcus infections in infancy and childhood are vaginitis and conjunctivitis. Rarely a urethritis is present in older boys. The finding of a Gram-negative biscuit-shaped diplococcus intracellular in pus from the eye or vaginal discharge makes it almost certain that the organism is a gonococcus. But it must be remembered that other Gram-negative cocci are occasionally found in the eye and vagina, and if there is any doubt the finding should be confirmed by cultural methods.

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CHAPTER VII

CEREBROSPINAL FLUID

Physiology.—Normally the cerebrospinal fluid is clear and colorless, with a specific gravity of 1.004 to 1.006. It is elaborated by the choroid plexus. There is a constant formation of the fluid, and about 120 to 140 c.c. are present at any one time in the child. The fluid circulates from the lateral ventricles through the foramina of Monro to the third ventricle, through the aqueduct of Sylvius to the fourth ventricle, thence into the central canal of the spinal cord and into the subarachnoid space through the openings of the roof of the cisterna magna. According to Weed, the fluid slowly seeps down into the spinal subarachnoid space behind the spinal cord and upward on its anterior surface and then flows rapidly upward about the base of the brain and again more slowly over the hemispheres. The circulation is facilitated by impulses from the vascular system. Recent work makes it seem probable that instead of a circulation of the cerebrospinal fluid it is a process of diffusion. According to Dandy the absorption of fluid takes place through the capillaries which abound in all the radicles of the subarachnoid space. The normal pressure of the cerebrospinal fluid in children in the recumbent position is 40 to 90 millimeters of water. There are many factors which influence this pressure. Weed and Hughson have shown that alteration in intracranial venous pressure effects alteration in the cerebrospinal fluid pressure in the same direction, but of less degree. They also showed that the pressure of the cerebrospinal fluid is considerably above that within the sagittal sinus. This explains why a puncture wound in the wall of the sagittal sinus may remain patent without the occurrence of hemorrhage, should the sinus be transfixed during puncture. In such a case, however, anything that causes a lowering of the cerebrospinal fluid pressure, such as withdrawal of fluid, will result in hemorrhage. The administration of solutions of various concentrations by vein or by mouth causes changes in the pressure. Hypertonic solutions lower the pressure and

cause the brain to shrink. Hypotonic solutions bring about a prolonged rise in pressure with marked swelling of the brain.

Cerebrospinal pressure is increased in all forms of meningitis, in brain hemorrhage, brain tumor, and in certain toxic conditions such as uremia.

Chemistry.—Chemically, the cerebrospinal fluid is composed of water with inorganic salts, chiefly sodium and potassium chlorid, calcium-phosphorus, and with dextrose, urea, uric acid, and protein in the form of albumin and globulin. The composition of the fluid is not constant, even in the same individual. It depends on the choroid plexus as a selective organ, allowing the passage of different substances at varying rates. This presupposes changes due to the ingestion of substances which affect the composition of the blood. Certain drugs such as insulin have also to be considered.

Function.—The most important function of the cerebrospinal fluid is mechanical. It acts as a water-bed buffer to support and protect the central nervous system against sudden shocks from without and against changes in intracranial pressure. By virtue of its salt and sugar content it is also probably concerned with the metabolism of nerve tissue.

In the following pages we will consider the indications and technic for securing specimens and the significant physical and chemical properties of the cerebrospinal fluid in health and disease.

TAPPING FOR CEREBROSPINAL FLUID

Indications.—*Therapeutic.*—(*a*) For the relief of symptoms of cerebral irritation or compression, such as muscular twitchings, convulsions or stupor, whether due to inflammation, hemorrhage, or neoplasm; also in the treatment of hydrocephalus.

(*b*) For the administration of antiserum against meningococcus, pneumococcus, tetanus bacillus or other infections, and for the administration of chemical substances such as tryparsamid, salvarsanized serum, etc.

Diagnostic.—In all forms of meningitis or suspected meningitis, poliomyelitis, encephalitis, brain or cord tumor, brain hemorrhage whether due to birth injury or other causes, syphilis, or convulsions of obscure origin. In other words, in almost all cases where a diagnosis

of brain or spinal-cord inflammation is made, or suspected, a spinal tap is indicated.

It must be recognized that a diagnosis of acute meningitis in infancy is not always easy, and that the condition may be missed entirely, especially since meningitis in young children is often secondary. Indeed, the onset of the affection usually is missed because the symptoms of the primary disease dominate the picture. It is only when the intracranial pressure has increased to the point where vomiting, full fontanel or convulsions appear that meningitis is suggested. Until the meningeal exudate appears over the base of the brain there is no stiffness of the neck. Inequality or sluggishness of the pupils are indications for a lumbar puncture in infants.

Technic.—*Cistern Puncture.*—The following method is the one used by those who advocate cistern puncture in this country. It is needless to emphasize the care with which this should be done, or the irreparable damage which may result from faulty technic. We believe that in children only urgent indications justify cistern puncture, and that it should be done only by experienced persons. Unless the child is very stuporous, he should be anesthetized.

The patient should be in the lateral position, with the head bent forward, thereby stretching the atlanto-occipitalis ligament. At the beginning of the lower third of the distance between the occipital protuberance and the spinous process of the axis, the skin is perforated exactly in the midline. The line which joins the point of puncture with the root of the nose points the direction of the needle. When one proceeds in this direction, the cistern is reached at a distance of about 1.5 to 2.5 centimeters in infants. In older children the distance is somewhat greater. Ayer thinks it best for the operator to rely on his tactile impressions produced when the needle overcomes the resistance offered by the ligament and dura and passes into the cavity of the cistern. This sensation is quite definite for one experienced in performing lumbar puncture. A regular lumbar puncture needle, exceedingly sharp and with a short bevel, is used. It is an advantage to have one graduated in centimeters.

Ventricular Puncture.—The scalp around the fontanel should be shaved and the usual sterile precautions taken. A regular lumbar puncture needle is introduced at the outer angle of the anterior fontanel.

The external auditory meatus is used as a point toward which the needle should be directed, and fluid is obtained at a depth of 2.5 to 4 centimeters.

Lumbar Puncture.—The patient should be lying on his side with the spine bent forward as far as possible to separate the spaces between the vertebræ. Sterile precautions should be observed. The second, third, or fourth lumbar space may be used. In infants it is best to enter in the median line, in older children laterally. The needle is inserted forward and upward until one "feels" that the dura has been punctured. It is well to collect the fluid in several clear, sterile test-tubes so that, should the patient jerk and the fluid become bloody, some one tube will still be clear.

NORMAL CEREBROSPINAL FLUID

Physical Characteristics.—*Appearance.*—Clear, colorless.

Pressure.—Forty to 90 millimeters of water.

Amount.—Normally 5 to 15 c.c. of fluid can easily be moved.

Film Formation.—Absent.

Cytology.—One to 20 cells which are lymphocytes or endothelial cells. A fairly accurate differential count may be made in the counting chamber, but the stained film of sediment gives the best results.

Protein.—This is present in the form of serum-albumin, and globulin. The ratio of albumin to globulin is 2 : 1. It is probably not constant. To determine the total protein quantitatively, the most accurate way is to find the total nitrogen, using a micro-Kjeldahl method. Then the total non-protein nitrogen is determined on the protein-free filtrate prepared by Folin and Wu's method. The difference is multiplied by 6.25 since there is 16 per cent of nitrogen in the protein molecule. In infants and children the amount of protein varies from 15 to 50 milligrams per 100 c.c.

Albumin.—The simplest qualitative test for the detection of albumin in cerebrospinal fluid is the nitric-acid-ring test. In a small tube 0.5 to 1 c.c. of fluid is carefully layered on an equal amount of concentrated nitric acid. With a normal amount of albumin present a thin white ring appears at the contact of the two liquids. With an increased amount of albumin, the ring increases in thickness and density. Determination of the albumin fraction is as important as that of globulin.

Globulin.—There are three good qualitative methods for detecting an increase in globulin in the cerebrospinal fluid.

Ross-Jones Test.—About 0.5 c.c. of a saturated ammonium sulphate solution is gently layered over an equal amount of cerebrospinal fluid in a small test-tube. If the globulin content is increased, a gray-white ring appears at the contact of the two liquids.

Pandy's Test.—One drop of cerebrospinal fluid is added to 1 c.c. of 8 per cent carbolic acid solution. If a blue-white cloud forms there is an increased globulin content.

Noguchi's Reagent.—A normal spinal fluid remains perfectly clear or becomes faintly opalescent. An increased amount of globulin or albumin produces a general turbidity or flocculation. The components of the reagent are (1) alcoholic extract of acetone-insoluble tissue lipoids (solution I), and (2) an aqueous solution containing in 1000 c.c. 0.5 c.c. acetic acid, 10 c.c. of a saturated solution of picric acid in absolute alcohol, 1.5 grams acid potassium phosphate, and 4 grams sodium chlorid (solution II).

Sugar.—The sugar content of normal cerebrospinal fluid is from 40 to 65 milligrams per 100 c.c.

The Folin and Wu method is the simplest for the quantitative determination of sugar in cerebrospinal fluid. The qualitative test is best done with Benedict's solution. Careful qualitative work must determine individual standards for the normal, increased, or decreased amounts of sugar in the cerebrospinal fluid. One of the best methods is that recommended by Schloss and Schroeder by which 5 c.c. of Benedict's solution and 12 drops of fluid are boiled for two minutes. With a normal amount of sugar present, the blue color changes to green and a small amount of red-brown sediment forms on cooling. With an increased amount of sugar present the color changes at once and the deposit forms quickly.

Normally the cerebrospinal fluid sugar is 40 to 65 per cent of the blood-sugar. This relationship is considered fairly constant by most workers. Parallel changes in the blood and cerebrospinal fluid have been noted in diabetes and after insulin injections. Our experience has shown that relative changes in the cerebrospinal fluid sugar have more diagnostic significance than absolute values without reference to the blood-sugar. In cases where the clinical diagnosis is certain, as in sup-

purative meningitis, it is not necessary to determine the blood-sugar for comparison. In such a case the absolute value of cerebrospinal fluid sugar will usually give the desired information. However, where the diagnosis is in doubt, as in differentiating between tuberculous meningitis, poliomyelitis, and encephalitis, the quantitative and comparative determination of sugar in blood and cerebrospinal fluid will often be of help.

Two cases are cited to show the value of simultaneous cerebrospinal fluid and blood-sugar determinations. In an infant with convulsions and an internal strabismus, encephalitis was a tentative diagnosis. A lumbar tap gave fluid under increased pressure with slight pleocytosis, slight increase in protein and marked increase in sugar. Quantitatively, the sugar was 115 milligrams per 100 c.c. One might feel justified in making a diagnosis of encephalitis on the above data, but the blood-sugar was found to be 216 milligrams, making the cerebrospinal fluid sugar 53 per cent of the blood-sugar which is a normal relation. The final diagnosis was tetany with a transient weakness of the sixth cranial nerve, high sugar in the blood and cerebrospinal fluid, and a slightly abnormal cerebrospinal fluid following a convulsion. Other cases of the same sort could be cited.

In the second case the diagnosis lay between tuberculous meningitis and encephalitis. The cerebrospinal fluid sugar was 71 milligrams per 100 c.c. and the cytology and protein reactions were not incompatible with either diagnosis. However, the blood-sugar was 250 milligrams per 100 c.c., making the cerebrospinal fluid sugar 28 per cent of the blood-sugar. This low ratio is characteristic of tuberculous meningitis. A few days later the clinical picture was more definite and tubercle bacilli were found in the fluid.

Chlorids.—In normal cerebrospinal fluid these range from 675 milligrams to 750 milligrams per 100 c.c. This is much higher than the blood-plasma chlorids. In comparing blood-plasma and cerebrospinal chlorids in 23 normal infants and children, we found an average difference of 147 milligrams. High or low blood chlorids usually caused a change in the same direction in the cerebrospinal fluid. However, the low chlorid content of purulent cerebrospinal fluid is not due to a lowering of blood chlorids, for here the latter are normal. On the other hand, in tuberculous meningitis, where the cerebrospinal fluid

chlorids are low, the blood-plasma chlorids are also low, though not in the same proportion.

In 24 cases of tuberculous meningitis there was an average difference between cerebrospinal fluid and blood chlorids of 99 milligrams as opposed to the normal difference of 147 milligrams. The cerebrospinal fluid chlorids were 11.7 per cent lower than normal, while the blood-plasma chlorids were only 6.6 per cent below normal. We believe that, within certain limits, a determination of blood and cerebrospinal fluid chlorids is a useful diagnostic procedure. Two good methods for determining chlorids are those of Van Slyke and of Whitehorn.

In normal cerebrospinal fluid (1) bacteria are absent, (2) the Wassermann reaction is negative and (3) the colloidal gold reaction is negative.

The colloidal benzoin reaction was introduced in 1920 by Guillain, Laroche, and Lichelle, who claim that it gives results as reliable as those obtained by the Wassermann and colloidal gold reactions, and that it is less subject to error than the colloidal gold reaction. The work done in this country does not seem to substantiate these claims (Warnock). Undoubted syphilitic cerebrospinal fluids do not regularly precipitate in any definite zone of dilution and many non-syphilitic cerebrospinal fluids do precipitate the suspension even in the so-called syphilitic zone. Reactions repeated on the same fluids do not give uniform results.

CEREBROSPINAL FLUID IN DISEASE

Meningismus.—By meningismus is meant a condition of meningeal or cerebral irritation evidenced by stiffness of the neck, Kernig's sign, twitching, convulsions, or stupor occurring in the course of any infectious disease or any toxic condition. It is frequently seen in pneumonia.

The cerebrospinal fluid in this condition is clear, often under increased pressure, and increased in amount. No film forms on standing. An increase in cells up to 90 per cubic millimeter may occur, but a normal count is the rule. The cells are mostly lymphocytes. The protein content is usually normal, but may be slightly increased, the qualitative tests for albumin and globulin being recorded as plus-minus, or

one plus. The quantitative protein is 20 to 50 milligrams per 100 c.c., occasionally going as high as 90 milligrams. The sugar is normal in amount, or increased, Benedict's test showing a one or two plus reduction, coming down promptly. The quantitative sugar is usually in the normal range, 40 to 60 milligrams, but may go as high as 90 to 100 milligrams. Since the blood-sugar is usually normal, the percental relation is high. Chlorids are normal, ranging from 675 to 750 milligrams per 100 c.c. The fluid is sterile, and the Wassermann and colloidal gold reactions are negative.

Acute Meningitis

Tuberculous Meningitis.—*Character.*—The fluid is usually clear and colorless. Rarely it is hazy or shows the ground-glass appearance.

Pressure.—Usually increased, especially at the first tap. Later taps may show normal or decreased pressure if blocking of the foramina in the cistern roof has occurred or if the process is largely plastic.

Amount.—At the first tap as much as 50 c.c. can easily be removed. Later the amount may be normal, increased, or decreased. The explanation of the lowered pressure and decreased amount of cerebrospinal fluid found sometimes in later taps is the fact that usually this is a basilar meningitis with blocking of the circulation of the fluid.

Film Formation.—Within six to twenty-four hours a web or film is formed. This is a delicate, colorless, weblike veil which is quite different from the heavy, yellowish coagulum formed rapidly in purulent fluids. It cannot be distinguished from the film which, in very rare cases, forms in the fluid of acute poliomyelitis. Therefore its presence, while practically diagnostic of tuberculous meningitis, is not absolutely so.

Cytology.—There is always a definite increase in cells and quite commonly a marked increase, the range being from 80 to 1000 per cubic millimeter. The majority of the cells are lymphocytes. Occasionally, polymorphonuclears will predominate throughout the course of the disease. The total number of cells increases with the progress of the disease, and as a rule the polynuclears also increase before death. Some workers believe that polynuclears occur early in the course.

Protein.—There is always a definite increase in protein in this condition. The qualitative tests for albumin and globulin are recorded one

plus to four plus, according to the stage and severity of the disease. Quantitatively, the range is from 100 to 1000 or more milligrams per 100 c.c. Sometimes the second tap shows less protein than the first, but succeeding taps show increasing amounts.

Sugar.—Benedict's solution is not normally reduced in this condition. Occasionally a faint reduction, coming down slowly, is reported, and very rarely, a normal reduction may be found which persists throughout the course. Quantitatively, the range is from 0 to 40 milli-

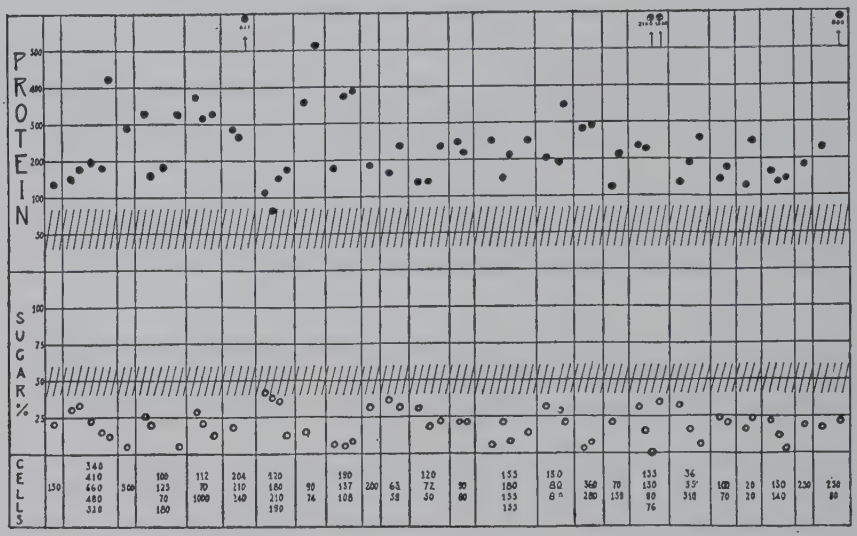

FIG. 15.—CHART SHOWING THE PROTEIN AND RELATIVE SUGAR CONCENTRATION OF CEREBROSPINAL FLUID IN 61 DETERMINATIONS ON 24 CASES OF TUBERCULOUS MENINGITIS.

The cross-hatching represents the normal range. All cases show a marked increase in protein and the low ratio of blood—spinal fluid sugar, characteristic in this condition.

grams per 100 c.c., or 0 to 35 per cent of the blood-sugar. While in most cases the sugar decreases in amount with the progress of the disease, it is too uncertain a factor to use in estimating the stage of the disease. Frequently first taps will give figures which are low normal, or just below normal, 35 to 45 milligrams per 100 c.c. It is here that a determination of blood-sugar is helpful. Blood-sugar in tuberculous meningitis is commonly high. So a low or even normal cerebrospinal fluid sugar and a high blood-sugar will give the low percental relation characteristic of this disease (Fig. 15).

Chlorids.—These are low, even early in the disease. They average 640 milligrams per 100 c.c., rarely going as high as a low normal. Blood chlorids are low also, but not as low relatively as those in the cerebrospinal fluid. Cerebrospinal fluid chlorids tend to decrease with the course of the disease. Occasionally higher chlorids will be found in the last stages of the disease than at the beginning.

Bacteriology.—The tubercle bacillus can practically always be found on careful search. Spreads are prepared by pouring the fluid over a slide held over a Petri dish, and the web spread out with platinum wires. The Ziehl-Neelsen carbolfuchsin method is used for staining. If it is not possible to find the bacilli in well-prepared slides, then the fluid in question should be injected intraperitoneally or intramuscularly into a guinea-pig. If the latter method is used, the neighboring lymph-nodes can be removed when involved and tubercle bacilli demonstrated in them. After intraperitoneal inoculation the guinea-pig may be killed in three or four weeks and tubercles demonstrated in the omentum, spleen, liver, and lymph-nodes. The tubercle bacillus can be grown on special media directly from the centrifugalized sediment of the cerebrospinal fluid. On all ordinary media there will be no growth.

Wassermann Reaction.—Negative.

Colloidal Gold Test.—There is usually a meningitic curve in the last tubes. The reaction is irregular and not at all characteristic.

Tuberculoma.—The spinal fluid in this condition is variable. If the tuberculoma does not touch the meninges, a normal fluid is to be expected. If, as is usually the case, a local or general meningitis occurs, the fluid is that of tuberculous meningitis.

Luetic Meningitis.—This condition is not common in infants and children, yet it does occur. It must be differentiated from encephalitis and tuberculous meningitis.

In untreated cases there is a clear, colorless, or, occasionally, a ground-glass fluid under normal or increased pressure, with a moderate increase in amount. As a rule no film forms on standing. The cell-count is increased, 30 to 100, rarely to 1000, all lymphocytes. There is an increase in protein in both the albumin and globulin fractions, the globulin being higher than the albumin. Quantitatively, the protein range is from 80 to 500 milligrams per 100 c.c. The qualitative tests for sugar usually show a normal reduction. Quantitatively, the sugar

is variable, but is usually normal or low normal, 35 to 50 milligrams per 100 c.c. Rarely, the sugar goes as low as 30 milligrams. Here tuberculous meningitis is ruled out by the blood, and cerebrospinal fluid, Wassermann reactions, and the bacteriological examinations.

Bacteriology.—On ordinary culture-media, the fluid remains sterile. Spreads from the fluid show no bacteria, nor are spirochetes demonstrable by Giemsa's stain. In order to demonstrate the *Spirochæta pallida* in the cerebrospinal fluid from cases of syphilitic meningitis, it is necessary to inoculate 2 to 5 c.c. of the fluid into the testicles of a series of rabbits. After a period of three to four weeks a characteristic lesion appears. From this lesion and the adjacent swollen lymph-nodes, spirochetes can be demonstrated under the dark field, and in culture by Noguchi's anaërobic method, using deep tubes with rabbit kidney to absorb the oxygen.

Chlorids are normal, 675 to 750 milligrams per 100 c.c. The blood and cerebrospinal fluid Wassermann reaction are positive, and the colloidal gold test gives a luetic curve.

In congenital lues without meningeal or brain involvement, the fluid is normal and the Wassermann and colloidal gold reactions are negative. Like Jeans, we have seen children with congenital lues who had no symptoms of cerebrospinal involvement, and whose cerebrospinal fluid showed no increase in cells or protein, yet gave a positive Wassermann reaction. This reaction is probable evidence of early disease of the nervous system. With successful treatment, the cerebrospinal fluid may slowly become negative. It may give positive reaction for years.

The laboratory findings in juvenile paresis and tabes are not different from those found in adults. There is a variable increase in cells, albumin, and globulin. The blood and spinal fluid Wassermann reaction are positive, and the colloidal gold test gives the typical luetic curves. In general paresis there is a reduction in the first 3 to 5 tubes, the curve reading 555 553 2000. In tabes dorsalis, and in cerebrospinal syphilis, a reaction occurs in the middle zone and is usually definite, that is, the color change is marked and the curve reads 002 345 4300. Any curve in the middle zone is called luetic.

Purulent Meningitis.—*Character.*—If the tap is done early, the cerebrospinal fluid may be only faintly cloudy or opalescent. The other

extreme is thick pus. The thickest exudate occurs in cases of influenzal meningitis. In pneumococcus meningitis the fluid has a greenish tinge.

Pressure is usually increased, and if the pus is not too thick, 40 to 60 c.c. can be removed.

Coagulum.—Thick and yellowish; it is formed within a short time.

Cells.—As many as 5000 or more, mostly polymorphonuclears, may be present.

Protein.—Qualitative tests for albumin and globulin may be four plus. Quantitatively, the amount goes as high as 5000 milligrams per 100 c.c or more.

Sugar.—Early taps may show a normal, or even an increased amount of sugar. The reason for this may be that the bacteria are not present in sufficient numbers to utilize the sugar. Another explanation may be that the choroid plexus in the early stage of the inflammation may allow the passage of certain substances at a faster rate than normally. The drop in the sugar later in the disease is due to the action of the bacteria or to the failure of the choroid plexus to allow its passage from the blood, or both. Partial or complete blocking of the circulation of the fluid may be another factor. The same theory may hold for the chlorids. When the disease is established, sugar is present in such small amounts that it is difficult to estimate it. With successful treatment, a decrease in the amount of protein and the cell-counts is coincident with an increase in the amount of sugar. Caffey, McLean, and Sullivan found a very low cerebrospinal sugar in 90 per cent of meningococcus meningitis before treatment. They conclude that increase in cerebrospinal fluid sugar during specific serum therapy is a favorable prognostic sign. Failure of cerebrospinal fluid sugar to increase during serum therapy in patients older than six months is an unfavorable prognostic sign. Failure of cerebrospinal fluid sugar to increase during serum therapy in patients younger than six months is not necessarily an unfavorable prognostic sign. Their chart shows the variations in sugar content during treatment (Fig. 16).

Chlorids.—Here again early taps may show a normal chlorid content, but usually they are low, varying from 600 to 650 milligrams per 100 c.c. The Wassermann reaction is negative, and the colloidal gold solution shows the meningitic curve; that is a change in the higher dilutions.

Bacteriology.—Suppurative inflammation of the cerebrospinal meninges in childhood is due to a variety of *pyogenic bacteria.* The meningococcus, the pneumococcus, the streptococcus, the influenza bacillus, the staphylococcus, the colon bacillus are, in our experience, found frequently in the order named. Neal's statistics show that, in infants

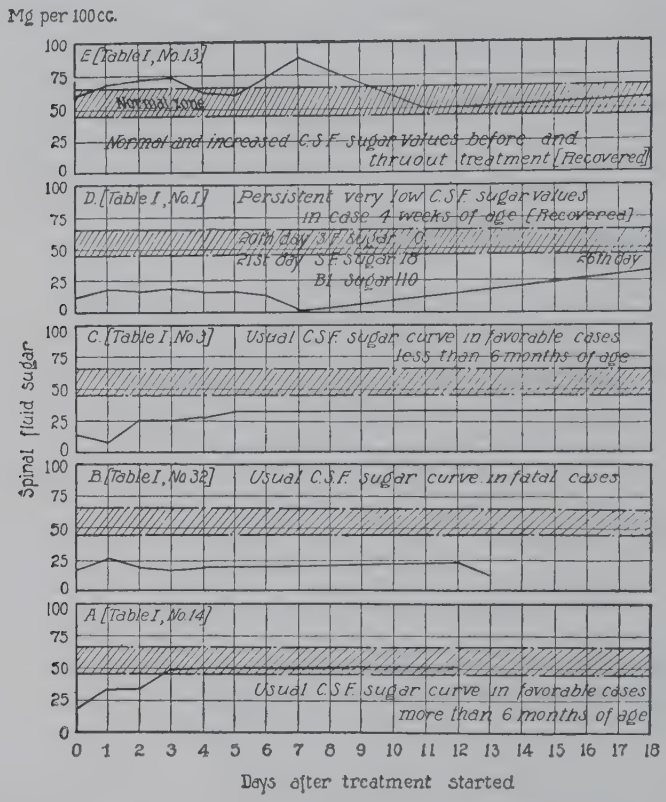
Mg per 100 cc.
E [Table I, No. 13]
Normal sugar
Normal and increased C.S.F. sugar values before and thruout treatment [Recovered]
D. [Table I, No. 1]
Persistent very low C.S.F. sugar values in case 4 weeks of age [Recovered]
20th day S.F. sugar 0
213t day S.F. Sugar 18
B.I. Sugar 110
261st day
C. [Table I, No. 3]
Usual C.S.F. sugar curve in favorable cases less than 6 months of age
B. [Table I, No. 3a]
Usual C.S.F. sugar curve in fatal cases
A [Table I, No. 14]
Usual C.S.F. sugar curve in favorable cases more than 6 months of age
Spinal fluid sugar
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Days after treatment started

Fig. 16.—Individual Case Variations in Cerebrospinal Fluid Sugar Curves During Treatment.

(From J. Am. M. Ass., June, 1927.)

under two years, the influenza bacillus is a more frequent cause of suppurative meningitis than is the pneumococcus. Rare cases may be caused by the *M. catarrhalis,* the gonococcus, *B. proteus, B. acidi lactici, B. typhosus.* In older subjects torula meningitis and streptothrix meningitis have been recorded.

Meningococcus Meningitis.—Meningococcus meningitis is the commonest form of suppurative inflammation of the meninges. It may

occur at any age, the youngest patient on record being seventeen days old.

The meningococcus was first isolated and grown in 1887 by Weichselbaum, who named it *Diplococcus intracellularis meningitidis*. As its name implies, it is often found within the polymorphonuclear leukocytes of the exudate, and grows in pairs. It also forms small groups. The cocci are biscuit-shaped and Gram-negative. They undergo degeneration rapidly, and thus they vary in size and staining power. Phagocytosis increases as the disease improves. The prognosis is better when the cocci are intracellular, because phagocytosis is an expression of immunity.

When the turbid cerebrospinal fluid from a case of meningococcus meningitis is allowed to stand in a test-tube for a half hour or longer, a precipitate of pus-cells forms. Spreads made from this precipitate, if allowed to dry in the air before fixation by heat and staining by Gram's method, will show the polynuclear leukocytes clearly, their outline, their nuclei and the contained cocci. The extracellular cocci are also clearly stained, lying in pairs or small groups, their flattened surface turned toward each other. The cocci tend to autolyze, and therefore they vary in size and in ability to take the stain. Cultures from meningococcus meningitis fluid must be made as soon as possible after withdrawal of the fluid because of this tendency of the cocci to dissolve. For the same reason large quantities must be planted, from 0.5 to 2 c.c.

The meningococcus grows best on vitamin-containing agar or broth enriched with ascitic fluid or blood, adjusted to a P^H of 7.6. Human or rabbit blood may be used, defibrinated or whole. On plates planted with 0.5 to 1 c.c. of fluid discrete colonies will usually appear after eighteen or twenty-four hours of incubation, and in a fairly profuse growth in forty-eight hours. In blood broth 1 to 2 c.c. of the fluid should be planted, and turbidity with a fair growth will be apparent in twenty-four to forty-eight hours.

It is not uncommon for the turbid or purulent fluid from a meningococcus case to contain so few cocci that a long-continued search in well-prepared spreads will result in the demonstration of only a single pair in many fields, or of a pale staining, swollen pair within a leukocyte. Cultures from such fluids may give no growth at all, because the cocci are not viable. In more than one instance we have been profoundly

grateful for the presence of one colony on two plates, for from that colony a subculture was made and the organism typed.

A purulent cerebrospinal fluid which contains no bacteria demonstrable in smears and culture is most apt to be meningococcic in type, since all other pyogenic cocci and bacilli are present in the cerebrospinal fluid in large numbers. After the administration of antimeningococcic serum the cocci grow less numerous and less viable, since the action of the serum is through its phagocytic and lytic power.

Four main groups of meningococci have been demonstrated by means of agglutination and agglutination absorption studies. According to Gordon, group I corresponds to the parameningococcus of Dopter, group II is the normal meningococcus, group III includes irregular strains related to I, and group IV contains irregular strains related to II. It is evident that immune bodies for all these groups must be represented in a polyvalent serum which is to be of value therapeutically. A great number of strains are used in the preparation of serum.

Meningococci find their way to the meninges through the blood stream or through the lymphatics from the upper respiratory tract. In 25 per cent (Elser and Huntoon) to 50 per cent (Herrick) of the cases, the meningococcus can be demonstrated in the blood during the early days of the disease. It is present in the nasal secretion of about half the cases, and about one-third of the patients remain carriers of the cocci for a variable period during convalescence. Studies made during the war brought out the important epidemiological fact that 38 per cent of contacts carried the organism in their nasopharynx, but the chronic carrier condition occurs in only about 1 or 2 per cent of the population.

The meningococcus does not occur outside of the human body. No intermediary host carries the infection, nor are domestic animals susceptible to it. In other words, every case of meningococcus meningitis is dependent upon a human being for infection. The low incidence of the disease can, apparently, only be explained by the phenomenon of individual resistance to the meningococcus, and this, for the majority of human beings, is high. In examining the nasopharyngeal secretions for meningococci the organism must be differentiated from related Gram-negative cocci, like the *Micrococcus catarrhalis. Micrococcus flavus,* and the *Micrococcus pharyngis.* This can be done by means of fermen-

tation tests in serological reactions. The appended table shows the reactions of the various Gram-negative cocci to sugars.

Meningitis due to the pneumococcus, *Diplococcus pneumoniæ* or *Micrococcus lanceolatus,* is, in our experience, the second most common form of suppurative meningitis in early childhood. The coccus occurs in pairs, the individuals being lance-shaped (pointed at one end) with the widest end turned toward its fellow. In fluid media short chains of three to six pairs are common, but the long interlacing chains which streptococci form in suitable fluid media are practically never made by the pneumococcus. The pairs are surrounded by a capsule which is readily seen in spreads made from the blood or fibrinopurulent exudates. It can be demonstrated by Welch's method with glacial acetic acid, or by the copper sulphate method of His. The coccus is Gram-positive. It grows best on ascitic fluid or blood vitamin agar or broth adjusted to a P^H of 7.6. Pneumococci ferment inulin, and most streptococci do not. Pneumococci are dissolved by bile and streptococci are not. Differentiation between pneumococci and streptococci is often impossible on morphological and cultural criteria, and the inulin and bile tests must be resorted to. Even then a few strains remain refractive, and serological tests must be made. On blood-media the pneumococcus colonies produce a greenish color due to the production of methemoglobin. Since the cocci form acid in the process of their growth they die rapidly in cultures.

The cerebrospinal fluid in pneumococcus meningitis is turbid at the onset and purulent at the end. A precipitate of pus-cells forms on standing. Spreads made therefrom show numerous Gram-positive, lance-shaped diplococci lying outside of polynuclear leukocytes. It is usually easy to find the characteristic cocci in the first field examined. In infants, pneumococci belonging to group IV are most often found in the meningeal exudate. Pneumococci of types I, II, and III are found far less frequently. Thus we have encountered 12 cases of group IV pneumococcus meningitis, one case of type III and one case of type I at the Babies' Hospital. The pneumococci from the blood stream, cerebrospinal fluid and sputum should be correlated in every case. At autopsy, cultures from the lung substance should be added to this list.

Pneumococcus meningitis may be primary, or it may be secondary to a bronchopneumonia or a lobar pneumonia. In young infants it may

be the terminal event in a pneumococcus sepsis with involvement of several other serous membranes.

Influenzal Meningitis.—The bacillus, which Pfeiffer described in 1892 after the great pandemic of influenza, is a slender rod, staining deeply at the poles, varying in size and shape. Thus it occurs in very short forms, in pairs, or in small groups. On dry culture-media it forms long threads and on media which are moist, or in fluid media, it often grows in swollen, irregular, bizarre forms. The bacilli are negative to Gram's stain. They are best stained by dilute carbolfuchsin (1:10). The polar granules can be well demonstrated by the fuchsin, dilute safranin, or Giemsa's stain.

The influenza bacillus grows best on blood agar (human or rabbit blood mixed with melted vitamin agar at 60° C.) and form dewdrop, colorless colonies which do not hemolyze. Avery showed that blood is not necessary for the growth of this organism in that certain plant substances are able to supply both the vitamin factor and the biocatalyst necessary for its growth.

To isolate the influenza bacillus from the throat or sputum Avery's oleate blood agar is most suitable, since it inhibits the growth of pneumococci and streptococci so that the influenza bacillus colonies grow larger than they do on other media.

The strains of this bacillus vary biologically in their ability to ferment sugars and to produce indol, serologically in their agglutinations, and pathogenically in their virulence for rabbits. The meningeal strains are most virulent, are closely related serologically, and produce indol. The cerebrospinal fluid from a case of influenzal meningitis often gives an odor of indol. It is turbid with a precipitate of pus, and it grows progressively thicker as the disease advances. Finally it becomes too thick to run through the needle. Spreads from the fluid show pus-cells and numerous Gram-negative bacilli varying in size, many suggesting colon bacilli. The first generation of such bacilli on blood-agar plates grow as delicate colonies often made up of the most bizarre shaped bacilli, curved, twisted, poled and globular. Subcultures from these colonies on vitamin blood agar-slants show the normal morphology of influenza bacilli.

In many cases influenzal meningitis is secondary to respiratory infection, and the bacilli can be grown from the nasopharynx and

sputum. In some instances it may be a primary disease. The blood-culture gives a positive growth of influenza bacilli in the great majority of cases.

Staphylococcus Meningitis.—Staphylococci are spherical bacteria which occur in clusters or small groups. In rapidly dividing cultures four elements may form a chain. The line of division is in the long diameter of the chain, not transversely as is the case in chains of streptococci. Staphylococci are Gram-positive. They grow well on plain agar. *Staphylococcus aureus* forms a golden yellow pigment, sometimes paler and slightly tinged with brown. *Staphylococcus albus* forms no pigment. As a rule, the *aureus* is more invasive than are the *albus* strains, but the latter may be the cause of fatal sepsis. We have seen ten cases of meningitis caused by *Staphylococcus aureus* and only one due to *Staphylococcus albus*. *Staphylococcus aureus* is the common cause of furuncles, carbuncles, osteomyelitis, abscesses, some cases of bronchopneumonia, empyema, and meningitis. Young infants are rather more often subject to staphylococcus than to streptococcus infections. The reason for this is the lack of immune bodies in the young infant's serum and the almost universal presence of staphylococci on the skin surface of the child and his attendants.

Staphylococcus meningitis is always secondary, and often the terminal event in a birth sepsis. The umbilicus or the upper respiratory tract may be the point of entrance. The cerebrospinal fluid is turbid with a precipitate of pus-cells. Spreads show polynuclear leukocytes, and many Gram-positive cocci in groups within and without the cells. The condition is always fatal.

Streptococcus Meningitis.—Streptococci are spherical bacteria which form chains of varying length and are Gram-positive. Division takes place in one direction only and within the chains the young cocci may be oval in shape and paired.

The broadest classification of streptococci is that which separates the hemolytic from the non-hemolytic strains. The former are more pathogenic or invasive for man, and include the streptococci of scarlet fever, inflamed throats, erysipelas, acute abscesses, sepsis and meningitis. Some non-hemolytic streptococci produce methemoglobin, causing a green color on blood-media, and are known as *Streptococcus viridans*. They are less invasive for man and cause less acute inflammations.

They are the cocci found in the blood and valvular vegetations in subacute endocarditis.

The cerebrospinal fluid in a case of streptococcus meningitis is turbid with a precipitate of pus. It is usually yellow in color in contrast to the slightly greenish tinge of the fluid due to pneumococcus invasion. Spreads show many polynuclear leukocytes and many Gram-positive cocci in chains. On blood-agar plates and in blood broth the growth is characteristic, and the hemolytic character plainly demonstrated. Streptococcus meningitis is always secondary. The primary lesion may be in the throat, ears or lungs. In young infants the umbilicus may be the point of entrance and other serous membranes may be involved.

Colon Bacillus Meningitis.—Meningitis due to the colon bacillus, either *B. coli communis* or *B. coli communior,* occurs in young infants in the first weeks of life, infected as a rule through the umbilicus. The purulent fluid has a grayish color, a large precipitate of pus-cells, and a distinct odor of indol, much stronger than is the odor of the fluid in influenzal meningitis. Spreads show polynuclear leukocytes and Gram-negative bacilli in fairly large numbers. The bacilli are usually two or three times as long as they are wide, occurring in pairs, in short chains or in small groups. The disease may last four to six weeks. The bacilli are readily grown on plain agar or in plain broth from the cerebrospinal fluid and from the circulating blood.

Suppurative meningitis in young children may be caused by a great variety of other bacteria than those just described. Cases have been recorded as caused by *B. typhosus, B. enteritidis* (Smith and Aberd), *B. acidi lactici* (Greenthal), *B. mucosus capsulatus* (Barron), *B. pyocyaneus, M. catarrhalis* (Garland). In older children streptothrix has been found in cerebrospinal fluid (Neal and Elmendorf) and torula has also caused meningitis in a case described by Neal and Shapiro. Repeated examination of spreads and cultures are required to establish the diagnosis.

Basilar Meningitis.—Chronic basilar meningitis is a late stage of meningococcus meningitis, and the character of the fluid depends upon the stage of the disease, that is, upon the character of the residual lesion at the base of the brain and within the ventricles.

The fluid is decreased in amount if blocking at the cistern is complete. When the exudative stage of the lesion is over only the produc-

tive sequelæ are present, the fluid is clear and colorless. A turbid fluid, either from the spinal canal or from the ventricles, means that an inflammatory focus is still present. The cells are increased sometimes up to 1000, polymorphonuclears predominating. The clear fluid shows cells only slightly more numerous than normal. The ventricular fluid may be more turbid than the lumbar fluid.

Protein.—The qualitative reactions for globulin and albumin vary from one to four plus. Quantitatively, the range is from 100 to 800 milligrams per 100 c.c. depending upon the stage of the lesion. There may be more protein in the ventricular than in the lumbar fluid because of stasis.

Sugar.—The sugar content is variable, being normal, or decreased. There may be a difference in the sugar content of the ventricular and lumbar fluids.

Chlorids.—These are usually normal in this condition, 675 to 750 milligrams per 100 c.c.

Bacteriology.—The fluid yields meningococci on smear and in culture, more readily if it be still turbid.

Colloidal Gold Test.—This gives a curve in the higher dilutions. In the late stages, where the exudate has disappeared, the fluid is almost normal, as is the case in any chronic hydrocephalus.

We know of no condition in children which justifies the name serous meningitis, unless it be the passing condition designated as meningismus. A serous inflammation of the meninges we have never seen at autopsy.

Neal has met with instances where a slightly cloudy fluid was obtained from children with otitis media. The fluid remained sterile, and after several days became clear and normal. This may have been due to a localized meningitis which resolved. One such case has come under our observation.

Brain Abscess.—The cerebrospinal fluid in this condition depends entirely on the amount of meningeal irritation, or involvement. Unless there is localized meningitis over the site of the abscess, the fluid shows no cytological or chemical changes although the intracranial pressure is increased.

Epidemic Encephalitis.—When we consider that the cerebrospinal fluid in this condition may be normal or may differ in no way from

the fluid in anterior poliomyelitis, polioencephalitis and meningismus, we get some idea of the difficulties of diagnosis in this condition. An increased amount of sugar in the cerebrospinal fluid, with a moderate increase in lymphocytes and protein, occurs in other conditions (bulbar poliomyelitis, meningismus, convulsions from any cause) and therefore is not diagnostic of encephalitis. A second lumbar puncture will usually aid the differential diagnosis by ruling out the other conditions. A sustained high sugar is a point in favor of encephalitis.

Cerebrospinal Fluid.—Occasionally the cerebrospinal fluid is clear under increased pressure, and usually increased in amount. Rarely, according to Neal, it is yellow or blood-tinged.

Cytology.—There is a moderate increase in cells, usually less than 100, rarely 1000. Lymphocytes predominate.

Protein.—A moderate increase in protein is the rule. The qualitative tests for albumin and globulin are from one to three plus. The quantitative findings are from 40 to 200 milligrams per 100 c.c.

Sugar.—Usually the amount of sugar is increased, both absolutely and relatively. The qualitative tests are reported one to four plus, the reduction coming down promptly. Quantitatively, the sugar is from 40 to 120 milligrams per 100 c.c. The blood-sugar is usually normal, making the percental relation high. Some workers, Thallheimer and Updegraff, have reported high blood-sugar in this condition, but it is not the rule. Halliday's reactions show that a normal relation between blood-sugar and cerebrospinal fluid sugar exists in encephalitis. Our results in infants do not agree with those of Halliday.

Chlorids.—These are in the normal range, 675 to 750 milligrams per 100 c.c.

The *Wassermann reaction* is always negative.

Colloidal Gold Test.—The curve is irregular and not characteristic.

In children, the fluid usually returns to normal in from ten days to two weeks. But an abnormal fluid (increase in cells, protein, and sugar) may persist indefinitely, with or without signs of clinical activity. The work of Peabody, Draper and Dochez showed that in poliomyelitis, the protein rises to a maximum in the third or fourth week, and may persist indefinitely into convalescence. Therefore, an increasing protein is in favor of a diagnosis of poliomyelitis, and when the fluid returns to normal quickly the diagnosis of encephalitis is the more

probable one. It is true that some cases of poliomyelitis, possibly the majority of them, show an increasing amount of protein up to the fourth week or later. But since the same thing may occur in undoubted cases of encephalitis, it cannot be considered diagnostic of poliomyelitis.

Lead Encephalitis.—This is a fairly common complication of lead poisoning in infants and children. The clinical picture is the usual one seen in lead poisoning, anemia, vomiting, peripheral nerve lesions, plus central nervous system symptoms, as irritability, twitchings or convulsions, stupor or behavior changes.

The cerebrospinal fluid is usually clear, with cells increased from 60 to 100, mostly lymphocytes, protein is definitely increased quantitatively up to 150 to 200 milligrams. The sugar is normal or high relatively and absolutely, and the chlorids are normal.

Anterior Poliomyelitis and Polioencephalitis.—These two conditions are caused by the same virus, according to its localization in the cord or in the brain.

In the acute stage, the fluid is clear, colorless, and under slightly increased pressure. Rarely, when taps are done in the first twenty-four hours, the fluid is opalescent, and still more rarely a film may form.

Cytology.—The cell count may go as high as 1000 or 2000 per cubic millimeter. Lymphocytes usually predominate, but cases have been recorded in which the fluid contained 70 to 80 per cent polymorphonuclear cells. Based on the observations of Peabody, Draper and Dochez, it has been stated that early in the disease there is an excess of polymorphonuclears which is later replaced by lymphocytes. Neal, in a series of cases in the 1916 epidemic, found polymorphonuclear cells predominating in only 39 cases, and some of these were found as late as the twenty-first and twenty-seventh day. She feels that the polymorphonuclears represent a special type of reaction, not a stage of the disease.

Protein.—Taps done in the first week show a variable increase in protein. The qualitative readings for albumin and globulin are recorded from one plus to three plus, and the quantitative protein may go from normal to 500 milligrams per 100 c.c. Occasionally, some cases show a progressive rise in protein, maximum in the third or fourth week. There is no relation between the cytology and protein content.

Sugar.—The content is variable. In the spinal type, a normal sugar is to be expected, that is, a one plus reduction of Benedict's solution, and quantitatively 40 to 65 milligrams per 100 c.c., with a normal relation to the blood-sugar. In the bulbar type, and in polioencephalitis, a high sugar is to be expected, much like the readings and figures we have in encephalitis.

Chlorids.—They are in the normal range, 675 to 750 milligrams per 100 c.c. The fluid is sterile, the Wassermann reaction is negative, and the colloidal gold curve is irregular and not characteristic.

On ordinary media these fluids are sterile. The virus of poliomyelitis is a filtrable, ultramicroscopic organism, first described and grown by Noguchi in 1911. In Giemsa-stained spreads from a pure culture the organism is seen to be minute, globoid, occurring in pairs that chain, or in groups. It grows under anaërobic conditions only. Intracerebral inoculation of live culture into the meninges of monkeys produces the symptoms and lesions of anterior poliomyelitis as it occurs in man.

Brain Tumor.—Cerebrospinal fluid in this condition is usually clear, but may be xanthochromic if the tumor reaches the surface of the pia-arachnoid causing congestion and hemorrhage. The pressure is increased. The fluid is increased in amount. There is no film formation.

Sugar.—This is normal or increased in amount.

Cytology.—Cell-count and protein are normal unless the meninges are involved.

Chlorids.—These are in the normal range, 675 to 750 milligrams per 100 c.c. The fluid is sterile, and the *Wassermann reaction* and *colloidal gold test* are negative.

Intraspinal Tumors.—The combination of xanthochromia, lymphocytosis, and massive coagulation, known as Froin's syndrome, is found in intraspinal tumors if they involve the cauda equina. At first it was thought that only fluid below the obstruction showed this syndrome, and, that as a result of stasis, the fluid approximated the blood-plasma in composition. But Cushing and Ayer have found the same sort of fluid above the obstruction with less marked changes.

Froin's syndrome has also been observed in a case of tuberculous meningitis with adhesions over the cervical cord and a consequent interference with the circulation. The syndrome is not always com-

plete; there may be no lymphocytosis; spontaneous coagulation may not always occur, but there is usually a definite increase in protein.

In localizing tumors, Cushing and Ayer have worked out a method which depends on the dynamics of the fluid. A complete description of the method has been given by Ayer.

To determine the type of hydrocephalus, the method of Dandy and Blackfan should be used. Phenolsulphonephthalein is injected into the ventricles, and if obstructive hydrocephalus is not present, the dye will appear in three minutes in the fluid obtained by lumbar puncture.

Miscellaneous Conditions.—In epilepsy, chorea, various types of idiocy, and hydrocephalus uncomplicated by chronic basilar meningitis, so far as we are able to determine with present methods, the cerebrospinal fluid is essentially normal. Occasionally increased cell-counts, protein and sugar have been reported, but we feel that such fluid must have been obtained soon after a convulsion.

In convulsions from any cause and in severe metabolic changes with cerebral symptoms such as acidosis, diabetic coma, and nephritis with uremic symptoms, the fluid is apt to deviate from the normal in that it contains an increased number of cells, an increased amount of protein and a high absolute and relative amount of sugar. In uremia the increase in protein is especially marked.

It must never be forgotten that the laboratory findings give additional facts which must be weighed in the making of a diagnosis, but only rarely are they so absolutely characteristic (such as finding tubercle bacilli in smears, or demonstrating spirochetes by the dark field) as to have the deciding vote in that diagnosis. Especially does this apply to the diagnosis of encephalitis. All toxic conditions with convulsions, especially those resulting from kidney lesions must be excluded before that diagnosis is justified.

Birth Injuries.—It is important in diagnosing intracranial hemorrhages to make sure that the blood in the cerebrospinal fluid is not due to trauma from the needle. When the needle trauma is slight, the first fluid is bloody, but the later fluid is increasingly clear. In intracranial hemorrhage, the fluid is uniformly bloody. On centrifuging a fluid with blood from trauma, the supernatant fluid becomes clear. If old blood is present, the fluid has a yellow tinge. Another point is that fresh blood from needle trauma coagulates quickly, while that

which has been in the cerebrospinal fluid for a time is slow to coagulate, or does not coagulate at all.

Differential Diagnosis

	Wassermann	Chlorids	Sugar	Protein
Meningismus convulsions	Negative	680–750 mg. Normal	40–100 mg. Normal or +	40–70 mg. Normal or +
Epidemic encephalitis ..	Negative	680–750 mg. Normal	40–150 mg. Normal or +++	40–100 mg. Normal or ++
Lead encephalitis	Negative?	680–750 mg. Normal	40–100 mg. Normal or +	100–400 mg. ++ or ++++
Anterior poliomyelitis .	Negative	680–750 mg. Normal	40–100 mg. Normal or +	60–100 mg. + to ++
Lues	++++	680–750 mg. Normal	40–60 mg. Normal	80–150 mg. + to +++
Brain tumor	Negative	750 mg. Normal	40–100 mg. Normal or +	40–70 mg. Normal or +
Tuberculous meningitis	Negative	500–650 mg. Low	0–40 mg. Low	100–400 mg. ++ to ++++

In the conditions listed in the table the clinical picture in all of them can be somewhat the same, especially this is true early in the course. And the spinal fluid examination up to a certain point is similar, that is, the fluid is clear, is under increased pressure, and the cell-count is increased.

What this table attempts to show is:

1. That the routine serology sometimes will detect syphilitic infections of the central nervous system. I have more than once seen on hospital service the first clue leading to the correct diagnosis of syphilitic meningitis given by the routine serology in a case previously diagnosed tuberculous meningitis, encephalitis, etc. As emphasized elsewhere, single serological tests do not make a diagnosis of syphilis. There is still some question as to whether cases of lead poisoning give positive serology in the absence of syphilis.

2. That the laboratory findings in tuberculous meningitis are characteristic. It is rare to find any other condition which will give you a clear fluid with such a marked increase in protein, a low absolute and especially a low relative sugar and low chlorids. But it must be

remembered that the final diagnosis rests on finding tubercle bacilli in the cerebral spinal fluid.

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CHAPTER VIII

CHEMICAL AND BACTERIOLOGICAL EXAMINATION OF BREAST AND COW'S MILK

WOMAN'S MILK

Colostrum.—The milk in the early days of lactation is quite different from the later milk. It is yellow, very rich in protein and undergoes a massive coagulation with heat. It contains colostrum corpuscles which give it its yellow color. Milk of this character lasts about one week, but it takes about one month for mature milk to develop. Holt says that under normal conditions the daily quantity of milk may be assumed to be as follows:

During the second week	13-18 ounces (400- 550 c.c.)
At the end of the first week	10-16 ounces (300- 500 c.c.)
During the third week	14-24 ounces (430- 720 c.c.)
During the fourth week	16-26 ounces (500- 800 c.c.)
From the fifth to the thirteenth week	20-34 ounces (600-1030 c.c.)
From the fourth to the sixth month	24-38 ounces (720-1150 c.c.)
From the sixth to the ninth month	30-40 ounces (900-1220 c.c.)

Various factors such as the age, acute illness, menstruation, diet, and drugs affect the composition of the milk, and these are considered in the volume on infant feeding.

The composition of woman's milk at different periods is shown in the table taken from Holt, Courtney and Fales.

PERCENTAGE COMPOSITION OF WOMAN'S MILK BY PERIODS

Period	Number of Analyses	Fat	Sugar	Protein	Casein	Albumin	Ash	Total Solids
Colostrum (1–12 days) ..	5	2.83	7.59	2.25	...	...	0.3077	13.42
Transition (12–30 days).	6	4.37	7.74	1.56	...	...	0.2407	13.39
Mature (1–9 months)....	17	3.26	7.50	1.15	0.43	0.72	0.2062	12.16
Late (10–20 months)	10	3.16	7.47	1.07	0.32	0.75	0.1978	12.18

The consideration of the different constituents is taken up in detail in Volume XII on infant feeding.

Bacteriology of Breast Milk.—Normally breast milk is bacteria-free. Occasionally a few organisms may be found coming from the external milk ducts.

In suppurative inflammation of the breast and in bacteriemia, bacteria may be found in the milk. Tubercle bacilli may be found in the milk in cases of tuberculosis, especially at periods when a bacteriemia is present, and if the breast is involved they are quite likely to be present.

COW'S MILK

The following table of the composition of cow's milk is taken from figures of the New York State Experiment Station.

Composition of Cow's Milk

Constituents	Jerseys	Holsteins	Average Good Herd Milk
Fat	5.61	3.46	3.50
Sugar	5.15	4.84	4.75
Protein	3.91	3.39	3.50
Ash	0.74	0.74	0.75
Total Solids	15.41	12.43	13.00
Water	84.59	87.57	87.50
Total	100.00	100.00	100.00

A detailed consideration of the constituents of cow's milk is given in Volume XII.

Bacteriology of Cow's Milk.—Milk is sterile in the udder of the healthy cow, but it is an excellent culture-medium and even when collected under the most favorable conditions a number of bacteria are found. The animal afflicted with pyogenic or bacterial systemic disease may have infected mammary glands, while even perfectly healthy cows harbor bacteria in the milk ducts and teats, contaminating even fresh milk to the extent of at least several hundred bacteria per c.c.

When kept at about freezing point the bacteria content of milk shows very little increase, but at higher temperatures the bacteria rapidly multiply until even in cold weather the number may reach 750,000 per c.c. (Park). A standard of cleanliness established in vari-

ous cities by the introduction of "certified milk" limits the number to 30,000 per c.c. Milk containing over one million bacteria to the cubic centimeter is certainly harmful to the average infant.

Milk is eminently fitted to convey the germs of infectious disease, being second only to water as a medium. On the other hand, bacterial growth is responsible for many changes which enhance or detract from its nutritive value. The bacteria most commonly concerned with lactic acid production are the *Bacillus lactis aërogenes* and *Streptococcus lacticus* (Heinemann).

Infectious Diseases Conveyed by Milk.—Chief among the milk-borne infectious diseases is *typhoid fever,* the infecting organism being *Bacillus typhosus.* Typhoid bacilli may live and actively proliferate in milk for as long as thirty days. While it is difficult to definitely place the blame by actual bacteriological proof for such responsibility, the suspicion is fostered by the fact that epidemics show a preponderance of cases among women and children.

Evidence gathered from a number of epidemics points to milk as the carrier of the infection in *scarlet fever.*

The ability of the *Bacillus diphtheriæ* to live and proliferate in raw milk has been definitely established, while a number of writers have reported the direct transmission of infection by the *Spirillum choleræ* through milk.

The *diarrheal diseases of infants,* occurring, as they more frequently do, in the summer months at which time the bacterial content of milk is especially high, are doubtless due to infection, although they cannot be ascribed to any given microörganism. A number of years ago, several epidemics of *streptococcus sore-throat* were traced to contaminated milk upon reasonably reliable evidence. Formerly, great importance was attached to the presence of excessive numbers of pus cells and leukocytes in milk. On general principles, such findings warrant careful veterinary inspection.

The transmission of *foot-and-mouth disease* to man from infected cattle has been definitely established, and *anthrax bacilli* were successfully isolated from a sample of milk two weeks after its withdrawal from the cow.

Because of its great importance, the question of the conveyance of *tuberculosis* has been extensively investigated and by the intraperitoneal

inoculation of rabbits and guinea-pigs with samples of milk the presence of tubercle bacilli from infected cows has been definitely established. Direct transmission from tuberculous disease of the udder is manifestly easy, and systemic infection, particularly pulmonary and gastro-intestinal, is evidently a source, the bacilli passing through the udder without evidence of local disease in the secreting gland. Young children are especially susceptible to infection by the bovine type of organism and it is certain that tuberculous milk is an etiological factor.

The diagnostic value of the *tuberculin reaction* cannot be overestimated, the failure of the test in diseased animals being rare.

Pasteurization of Milk.—Milk or cream should be heated to a temperature of at least 142° F. and held at such temperature for thirty minutes or more. The advantages of such milk over raw milk for infant feeding have been definitely established, the reduction in the number of cases of diarrheal diseases being especially noticeable.

Estimation of the Number of Bacteria.—The counting of colonies on agar or gelatin plates is the usual method. The specimens are secured with care from well-mixed contents of can or bottle and transferred to a sterile test-tube or flask with a sterile pipet. After an initial dilution of say 1 : 100 is made, properly cooled tubes of culture-medium are inoculated. The plates are poured and the colonies are counted after twenty-four to forty-eight hours at room temperature or in the incubator. Proper calculations are then made, depending on the amount of dilution used.

Direct Methods of Counting Bacteria.—With a capillary tube, exactly 0.01 c.c. of the specimen is spread over a square centimeter on a microscopic slide. It is dried in the air and fixed with methyl alcohol, after which the fatty constituents can be dissolved with xylol. It can then be stained lightly with Jenner's stain, and the bacteria in a microscopic field covering 0.02 square millimeter counted. Calculations are then made.

The accompanying table represents an example of the manner in which the problem of market-milk control is handled. It is not a specific regulation for the grading of milk. Such regulations vary in different states and cities and in the same communities from time to time.

Bacteriotherapy.—The administration of lactic acid producing bacteria to patients suffering from intestinal putrefaction, as suggested

The following classifications apply to milk and cream. The regulations regarding

GRADES OF MILK OR CREAM WHICH MAY BE SOLD IN THE CITY OF NEW YORK	DEFINITION	TUBERCULIN TEST AND PHYSICAL CONDITION	BACTERIAL CONTENTS
GRADE A Milk or Cream (Raw)	Grade A milk or cream (raw) is milk or cream produced and handled in accordance with the minimum requirements, rules and regulations as herein set forth.	1. Only such cows shall be admitted to the herd as have not reacted to a diagnostic injection of tuberculin and are in good physical condition. 2. All cows shall be tested annually with tuberculin and all reacting animals shall be excluded from the herd.	Grade A milk (raw) shall not contain more than 60,000 bacteria per c.c. and cream more than 300,000 bacteria per c.c. when delivered to the consumer or at any time prior to such delivery.
Milk or Cream (Pasteurized)	Grade A milk or cream (pasteurized) is milk or cream handled and sold by dealers holding permits therefor from the Board of Health, and produced and handled in accordance with the requirements, rules and regulations as herein set forth.	No tuberculin test required but cows must be healthy as disclosed by physical examination made annually.	Grade A milk (pasteurized) shall not contain more than 30,000 bacteria per c.c. and cream (pasteurized) more than 150,000 bacteria per c.c. when delivered to the consumer or at any time prior to such delivery. No milk supply averaging more than 200,000 bacteria per c.c. shall be pasteurized for sale under this designation.
GRADE B Milk or Cream (Pasteurized)	Grade B milk or cream (pasteurized) is milk or cream produced and handled in accordance with the minimum requirements, rules and regulations herein set forth and which has been pasteurized in accordance with the requirements and rules and regulations of the Department of Health for pasteurization.	No tuberculin test required but cows must be healthy as disclosed by physical examination made annually.	No milk under this grade shall contain more than 100,000 bacteria per c.c. and no cream shall contain more than 500,000 bacteria per c.c. when delivered to the consumer or at any time after pasteurization and prior to such delivery. No milk supply averaging more than 1,500,000 bacteria per c.c. shall be pasteurized in this city for sale under this designation. No milk supply averaging more than 300,000 bacteria per c.c. shall be pasteurized outside of this city for sale under this designation.
GRADE C Milk or Cream (Pasteurized) (For cooking and manufacturing purposes only)	Grade C milk or cream is milk or cream not conforming to the requirements of any of the subdivisions of Grade A or Grade B and which has been pasteurized according to the requirements and rules and regulations of the Board of Health or boiled for at least two (2) minutes.	No tuberculin test required but cows must be healthy as disclosed by physical examination made annually.	No milk of this grade shall contain more than 300,000 bacteria per c.c. and no cream of this grade shall contain more than 1,500,000 bacteria per c.c. after pasteurization.

NOTE—Sour milk, buttermilk, sour cream, kumyss, matzoon, zoolac and similar products shall not be made from any milk of a less grade than that designated for "Grade B" and shall be pasteurized before being put through the process of souring. Sour cream shall not contain a less percentage of fats than that designated for cream.

No other words than those designated herein shall appear on the label of any container containing milk or cream or milk or cream products except the word "certified" when authorized under the State laws.

The term "certified" milk is usually defined for each region by a special commission of the

bacterial content and time of delivery shall not apply to sour cream.

NECESSARY SCORES FOR DAIRIES PRODUCING	TIME OF DELIVERY	BOTTLING	LABELING	PASTEURIZATION
Equip. 25 Meth. 50 Total 75	Shall be delivered within 36 hours after production.	Unless otherwise specified in the permit this milk or cream shall be delivered to the consumer only in bottles.	Outer caps of bottles shall be white and shall contain the words Grade A, Raw, in black letters in large type, and shall state the name and address of the dealer.	
Equip. 25 Meth. 43 Total 68	Shall be delivered within 36 hours after pasteurization.	Unless otherwise specified in the permit this milk or cream shall be delivered to the consumer only in bottles.	Outer caps of bottles shall be white and shall contain the words Grade A, in black letters in large type, date and hours between which pasteurization was completed; place where pasteurization was performed; name of the person, firm or the corporation offering for sale, selling or delivering same.	Only such milk or cream shall be regarded as pasteurized as has been subjected to a temperature averaging 145° F. for not less than 30 minutes.
Equip. 20 Meth. 35 Total 55	Milk shall be delivered within 36 hours and cream within 48 hours after pasteurization.	May be delivered in cans or bottles.	Outer caps of bottles containing milk and tags affixed to cans containing milk or cream shall be white and marked "Grade B" in bright green letters in large type, date pasteurization was completed, place where pasteurization was performed, name of the person, firm or corporation offering for sale, selling or delivering same. Bottles containing creams shall be labeled with caps marked "Grade B" in bright green letters, in large type and shall give the place and date of bottling and shall give the name of person, firm or corporation offering for sale, selling or delivering same.	Only such milk or cream shall be regarded as pasteurized as has been subjected to a temperature averaging 145° F. for not less than 30 minutes.
Score 40	Shall be delivered within 48 hours after pasteurization.	May be delivered in cans only.	Tags affixed to cans shall be white and shall be marked in red with the words "Grade C" in large type and "for cooking" in plainly visible type, and cans shall have properly sealed metal collars, painted red on necks.	Only such milk or cream shall be regarded as pasteurized as has been subjected to a temperature averaging 145° F. for not less than 30 minutes.

County Med. Soc., sanctioned by State Law. The following is the definition of certified milk given by the Milk Commission of Kings County, N. Y.:

CERTIFIED MILK must have every characteristic of pure, clean, fresh, wholesome cow's milk. The milk must be in its natural state, not having been heated and without the addition of coloring matter or preservatives. Nothing must be added to the milk and nothing taken away.

CERTIFIED MILK shall not contain less than 4 per cent of butter fat.

* Table taken from Rules and Regulations of N. Y. City Department of Health, 1914, applying to sale of milk and cream.

by Metchnikoff in 1906, has been extensively practiced and often with remarkable success. *Bacillus acidophilus* has largely displaced *Bacillus bulgaricus* for this purpose in America. Such therapy requires reinoculation from day to day to be successful. Changes in the intestinal flora are more definitely accomplished if the bacteriotherapy is combined with rational dietary adjustment, just as with feeding of yeast which functions in a similar manner.

CHAPTER IX

BLOOD CHEMISTRY IN PEDIATRICS

GENERAL CONSIDERATIONS

Since this is written for the practitioner no attempt will be made to take up in detail all the work that has been done on the chemical constituents of the blood. Nor will all the conditions in which changes in the blood chemistry may occur be considered. The conditions where the man in practice may expect help in diagnosis, prognosis or treatment from chemical analysis of the blood, are nephritis and disturbances of kidney function, diabetes and glycosuria, changes in acid base equilibrium and rickets and tetany. Now all of these conditions can be diagnosed and treated without blood analysis. Most of them in infants and children are managed with little or no help of this sort from the laboratory because one hesitates to do a venepuncture on a baby or child. Yet I believe that in a case of nephritis the blood chemistry gives more accurate information as to kidney function upon which treatment and prognosis can be based than do the ordinary means used. Blood analysis will be of help in the differential diagnosis between encephalitis and uremia. A blood-sugar determination is necessary in getting at the cause of a glycosuria. Impending coma in diabetes is not always easy to diagnose clinically, but a determination of the acetone bodies and the carbon dioxid combining power puts the physician in a better position at once. In infants with acidosis and dehydration a determination of serum protein, the carbon dioxid combining power and the non-protein nitrogen constituents will show accurately the severity and type of the acidosis, how far the kidney function has failed and the degree of concentration. It should also be of help in starting treatment. The cause of convulsions in infants is often difficult to ascertain. The determination of the serum calcium will make or rule out the diagnosis of tetany in doubtful cases.

We will consider briefly the various constituents of the blood, which are of clinical interest, and then take up the conditions where

changes in the blood chemistry occur. Some general considerations may be taken up at this point.

Technic of Venepuncture.—In most cases, even in very young infants, blood is most easily obtained from one of the veins of the arm. A tourniquet may be used to make the vein stand out, but should be removed as soon as the needle has entered the vein. Many prefer the external jugular vein. Venepuncture in infants and children is difficult because of the lack of coöperation, because of the low venous pressure and the fact that the veins are situated in loose areolar tissue with not much support. One is tempted to use narrow gauge needles but an 18 or 19 gauge needle will be more successful.

Technic of Sinus Puncture.—The longitudinal sinus is frequently used for drawing blood, giving infusions, etc. In experienced hands it is a perfectly safe method. The area about the fontanel should be washed and shaved and the usual sterile precautions taken. The anterior or posterior angle may be used. If a short needle is used and is inserted in the center of the sinus there is little danger of transfixing the sinus. The baby is wrapped like a mummy, the nurse holds the head between two hands and the doctor with the index finger of the left hand in the posterior angle of the sinus, using the nose as a guide to "line up" the exact center of the sinus, inserts the needle slowly at an angle of about 45 degrees. With a short needle one can go in almost perpendicularly without danger. The needle is felt to go through the skin and the tough dura, and usually there is enough pressure for the blood to push up the plunger of the syringle a little. Blood should be withdrawn slowly.

Time of Taking Blood.—In infants, blood should be taken just before a feeding, in older children just before breakfast. This is done in order to obtain clear serum for certain procedures, and because normal figures are for fasting blood. In interpreting results, account should always be taken of the character of the diet, drugs being taken such as insulin or adrenalin, and any other factors that may influence the blood chemistry. In doing research work, blood is often collected under mercury or oil, but for clinical work this is not necessary. Analysis should be made promptly after the blood is withdrawn.

Anticoagulant.—Fine-powdered potassium oxalate is satisfactory, about 20 milligrams to 10 c.c. of blood. If too much is used it inter-

feres with the protein precipitation, and the uric acid determination. Folin claims lithium oxalate (50 milligrams is enough for 20 c.c. of blood) has certain advantages.

Normal Blood Chemistry Values in Infants and Children

N. P. N.	25- 30 mg. per 100 c.c.
Urea N.	7- 15 mg. per 100 c.c.
Uric acid	3- 4 mg. per 100 c.c.
Creatinin	1- 2 mg. per 100 c.c.
Total plasma protein	6.5-7.5 per cent
Albumin	4.0-5.0 per cent
Globulin	1.5-2.5 per cent
Fibrinogen	0.2-0.5 per cent
Chlorids	
Whole blood	450-500 mg. per 100 c.c.
Plasma	550-620 mg. per 100 c.c.
Calcium (serum)	10- 12 mg. per 100 c.c.
Phosphorus (serum)	4- 5 mg. per 100 c.c.
Sugar	80-120 mg. per 100 c.c.
Cholesterol (W. B.)	140-170 mg. per 100 c.c.
CO_2 combining power	45- 60 volume per cent
Acetone bodies	5- 8 mg. per 100 c.c.
Lactic acid	10- 15 mg. per 100 c.c.

NITROGENOUS COMPOUNDS

Non-Protein Nitrogen.—The non-protein nitrogen of the blood consists of the nitrogen in urea, uric acid, creatinin, creatin, ammonia and amino-acids. After the proteins of the blood have been precipitated and the nitrogen in the above metabolites determined, a quantity of nitrogen remains which has been called rest nitrogen. It forms about 46 per cent of the non-protein nitrogen. It is not known what this nitrogen is nor what significance it has. The amount varies in certain diseases and with the method of precipitating protein.

Normal non-protein nitrogen values for adults are given at 20 to 40 milligrams per 100 c.c. In infants and children figures as low as 15 to 20 milligrams are frequent. It has been shown that the level of the non-protein nitrogen in the blood varies with the nitrogen metabolism. In a child under ten years of age figures above 30 milligrams are rarely found, and cannot be considered normal. The low figures are

simply the expression of the low nitrogen metabolism that obtains at this age and do not mean disease.

Urea.—Urea is the chief end product of protein metabolism, both endogenous and exogenous. Folin's figures for normal young adults are for urea nitrogen from 8.9 to 15.2 with an average of 11.5 milligrams per 100 c.c. For infants and children the figures are slightly lower. In health the urea nitrogen is about one-half the total non-protein nitrogen. In most conditions where there is nitrogen retention the proportion is higher, sometimes as high as 80 per cent. The question comes up as to which is preferable, a non-protein nitrogen or urea nitrogen. It is true that urea is a single chemical substance, but Folin thinks that the non-protein nitrogen determination is more reliable and our experience is in agreement.

Uric Acid.—Uric acid is also endogenous and exogenous in origin. Some of it comes from the breakdown of the nucleoprotein of the tissue cells and some from the purins in the food. The normal values range from 0.7 to 3.5 milligrams per 100 c.c. It is somewhat higher in the plasma than in the whole blood. The level of uric acid in the blood does not vary much whether the diet is rich or poor in purins. Starvation is said to raise the level somewhat. There are many questions connected with the uric-acid problem which are not yet settled, and one should be careful in interpreting abnormal values.

Creatinin.—According to Behre and Benedict, creatinin is not present in the blood in any appreciable amount. The figure they give is 0.05 milligram per 100 c.c. instead of the usually accepted 0.5 to 1.5 milligram. This question is still unsettled. However, the clinical value of the "creatinin" determination done by the usual methods remains the same. We have found in infants and children that a creatinin above 1.8 milligram per 100 c.c. is accompanied by other signs of impaired kidney function.

Ammonia, creatin, and the amino-acids, while interesting from a scientific standpoint, have little clinical interest as yet, and will not be considered here.

Serum and Plasma Proteins.—Normally the total protein in serum is between 7 and 8 per cent. Of the total, the albumin will be from 4.5 to 6.5 per cent, and the globulin between 1.9 and 2.2 per cent. Plasma contains in addition to albumin and globulin, fibrinogen 0.2

to 0.33 per cent. The total serum protein is of interest to pediatricians in cases of dehydration and acidosis. In cases of nephritis the total protein, and the relation of the albumin, globulin and fibrinogen fraction are important. There are other conditions where changes in the protein of the blood occur. It is possible that in some of these conditions, infection, neoplasms, liver disease and anemias, the determination of the protein and its fractions may be of some use clinically. Their value is doubtful at this time.

MINERAL COMPOUNDS

Calcium.—The normal serum-calcium content is between 9 and 12 milligrams per 100 c.c. and in health this varies very little. Feeding calcium salts will raise the level of serum calcium only when that level is low. With a normal calcium any excess of calcium in the diet is quickly eliminated. A certain amount of calcium in the blood is present in the un-ionized state. This non-diffusable portion (30 to 40 per cent) is probably bound up with the protein. The corpuscles contain little or no calcium.

Inorganic Phosphorus.—This should be determined on the serum or plasma, and should be done promptly since some of the organic phosphate changes over to the inorganic on standing. More of the inorganic phosphate is present in the corpuscles than in the serum. The normal value for adults is 3 milligrams per 100 c.c. with not much variation. In infants and young children 4 to 5 milligrams per 100 c.c. is normal. According to Hess, there is a seasonal variation of the phosphate in infants. From a maximum of 4.5 milligrams in June it falls to 4 milligrams in December and 3.5 milligrams in March.

Chlorids.—Chlorids are higher in the plasma than in the corpuscles. For whole blood 450 to 520 milligrams, and for plasma 550 to 610 milligrams per 100 c.c. are the normal figures. Ordinarily a fall in the cell volume will mean a rise in the chlorid content. Normally the concentration of chlorids is quite stable.

Bicarbonate.—The bicarbonate content of the plasma is the measure of the alkaline reserve of the blood and probably of the entire body. This will be considered later.

Other inorganic substances are present in the blood (magnesium, potassium, sodium, sulphate) but their clinical value has not been

thoroughly worked out. The inorganic constituents are not equally divided between corpuscles and plasma, and most of these determinations are better done on serum or plasma.

ACETONE BODIES, FAT AND CHOLESTEROL

Acetone Bodies.—Normally acetone, β-oxybutyric and diacetic acid are present in very small amounts in the blood, not more than 3 to 8 milligrams per 100 c.c. when measured quantitatively, and when tested qualitatively there is no reaction.

Fat.—Fat is present in normal serum or plasma in very small amounts. There is practically no fat in the corpuscles. After ingestion of fat there is a transient increase in blood-fat.

Cholesterol.—Normal values for cholesterol in plasma or serum are 150 to 190 milligrams per 100 c.c., and for whole blood 140 to 180 milligrams per 100 c.c. Bloor gives somewhat higher figures. After a meal with fat there is a moderate rise in the blood cholesterol, but it falls to the normal level in eight to twelve hours. A low fat diet will cause a drop in the blood cholesterol. According to Gordon and Cohn there is a variation with age. They found the lowest values to be 89 milligrams per 100 c.c. in cord blood and during the first week of life. At one year it was found to be 136 milligrams and from then on a gradual rise, 155 milligrams at the fourth year, and 169 milligrams at the sixth year.

WATER METABOLISM

Water enters intimately into the metabolism of all foods, as seen in its solvent action in helping the ingestion of foods, its hydrolytic action in the digestion of foods, again its solvent action in the elimination and secretion of the end products of digestion, also as a vehicle by which it dissolves substances in the blood stream. And an important additional function of water is seen in the regulation of temperature by the evaporation of water from the skin. When the balance is upset we have anhydremia on the one hand, and the different manifestations of edema on the other.

Water Requirements.—These have been shown to be:

Three ounces per pound (200 c.c. per kilogram per twenty-four hours) first three months.

Two and one half ounces per pound (per twenty-four hours or 150 c.c. per kilogram) three to twelve months.

Underweight infants require more, temperature increase indicates increase water intake as there is also excessive loss of fluid.

Course of Water in the Body.—This may be traced as follows:

1. Enters by mouth alone or mixed with food.

2. In the stomach acts as a solvent and diluent for foods, practically no absorption in the stomach.

3. In the intestinal tract about 90 per cent is absorbed and 10 per cent is excreted in the feces as a diluent of the intestinal content.

4. The absorbed water. Water absorbed from the intestine into the blood from which it is taken into the tissues. Water thus absorbed into the tissues may be:

(*a*) Reëxcreted in the intestine by the glands of digestion and this may be repeated. This absorption reëxcretion may be repeated more than once.

(*b*) Excreted and reabsorbed partially in the kidneys as urine containing urea, creatinin, phosphates, sodium chlorid, etc., in solution.

(*c*) Cutaneous glands excrete water on to the skin where it acts as a regulator of temperature. This sweat also contains some nitrogenous and salt products. Twenty-five per cent water ingested is said to be excreted through the skin.

(*d*) Excreted through the lungs, 1 per cent to 6 per cent normally. Thirst is possibly due to osmotic pressure changes in the intestinal cells. Water is stored in the body chiefly in the subcutaneous tissues, muscles and liver and the first classical indication of dehydration or loss of fluids is seen in the loss of skin turgor, which is, of course, due to a draining of the normal subcutaneous content. The condition of negative water balance or dehydration is one of extreme importance in pediatrics and the diarrheal diseases of early infancy. A negative water balance may be due to excessive perspiration as seen in exposure to high temperatures, excessive urination as seen in diabetes, and excessive diarrhea as seen infantile infections.

Dehydration.—The results in the body of excessive loss of fluids or dehydration are:

1. Loss of weight.

2. Increase in the concentrations of all components of the blood,

some of which are toxic, giving rise to acidosis and uremia. A very important result of a negative water balance in infants is that seen in kidney function. The kidney excretion is very markedly depressed, sometimes a complete anuria resulting. The failure of kidney in its normal excretion results in abnormal concentrations of N. P. N. (non-protein nitrogen) and other nitrogenous products causing uremia. Physiologically, probably, the kidney failure is in the main circulatory. There is a general depression in blood volume, lower kidney-blood-volume flow and capillary stasis. In general this is a circulatory failure in the kidney which impairs excretion.

The conditions in which changes in blood chemistry occur will be taken up in the following order:

1. Nephritis and disturbances of kidney function
2. Disturbances of carbohydrate metabolism
3. Disturbances of acid-base equilibrium
4. Rickets and tetany

There are many other conditions where changes in the blood chemistry may be expected to occur. Diet and fluid intake, fever, infections, terminal conditions, the anemias and blood dyscrasia, and other conditions, all have an influence on changes in the blood chemistry. In the newborn period the non-protein nitrogen constituents are likely to be somewhat elevated and the sugar somewhat lower than the normal values given for children. Other changes in the blood in this period are noted above. In cardiac disease with decompensation and in some postoperative cases there may be various degrees of impaired kidney function without an actual nephritis being present. This may be reflected in the blood chemistry, a moderate degree of nitrogen retention and some changes in the acid-base equilibrium. In calculi of the urinary tract, we sometimes get a reflex inhibition of kidney function with blood chemistry changes that accompany severe renal insufficiency.

NEPHRITIS IN CHILDREN

No attempt can be made here to give a thorough review of this subject, or to go into detail concerning the enormous amount of data that has accumulated. No apology is made for the classifications given here. They have served to group the cases, and they are simple, and until

we have more knowledge of the etiology and pathogenesis of these conditions, it makes little difference what name is attached.

We must realize that nephritis is seldom purely glomerular or purely tubular. When we use the term glomerular nephritis, we mean that the damage is predominantly glomerular. It is usually accompanied by more or less tubular injury, but this last is so slight that it does not give rise to the symptoms or laboratory findings that we associate with tubular nephritis.

In children, the clinical and laboratory findings point more clearly to the anatomical changes and there are fewer complicating features. Vascular disease is not frequent, and the cardiorenal complex is not met with so frequently.

Elaborate laboratory diagnosis is not as applicable to the child at home as in the hospital. Frequent venepunctures do not impress parents favorably. And it may be argued that when all the complicated blood analyses are made we know little more about diagnosis, prognosis, and treatment than the experienced clinician has gotten from a careful history, repeated physical examinations, and simple laboratory work. But in our experience the blood-picture has frequently given us more accurate information about kidney function than the clinical and urinary picture alone, and in many cases has given us a truer insight into the nature of the nephritis.

Acute Nephritis.—The following groups are recognized:

1. Acute glomerular nephritis (hemorrhagic)
   (*a*) Mild focal glomerulitis
   (*b*) Severe diffuse glomerulitis
2. Acute tubular nephritis (parenchymatous)
3. Acute mixed glomerulotubular nephritis

Most of the acute nephritides in childhood will fall into the above groups. But there are other forms. An acute purulent nephritis is met with, and acute luetic nephritis is probably more common than most clinicians realize. Acute nephritis due to chemical poisoning and burns must also be mentioned. And the question of febrile albuminuria comes up.

It is not uncommon to find albumin with or without red and white blood-cells, hyaline and granular casts in the urine of sick infants and

children. Careful examination of the urine in cases of tonsillitis, pneumonia, any of the acute exanthemata, diphtheria, intestinal toxemia, pyelitis, otitis, meningitis and rheumatism will show in many of the cases some evidence of kidney irritation. Kidney-function tests may be normal or may show some impairment of function. It is difficult to say whether this should be called acute nephritis. Parsons believes that this is the mildest form of acute nephritis, hemorrhagic or glomerular in type. Cohn found a marked increase in non-protein nitrogen in 34 of 55 cases of croupous pneumonia. It is probably better to look upon febrile albuminuria as acute nephritis and manage the case accordingly. The condition should not be stressed to the parents.

1. *Acute Glomerular (Hemorrhagic) Nephritis.* — (A) Mild Focal Glomerulitis.—This type of nephritis is found in any form of septic infection, and is perhaps met with most commonly as a complication of infectious endocarditis. But it can and does occur following pneumonia, tonsillitis, or any of the streptococcal infections. Volhard believes that this is a focal disease of the kidney, that occasional glomeruli are constantly being damaged while the vast majority of them remain intact. There is no edema, no increase in blood-pressure, and usually the children feel well. Kidney function tests are normal and the blood chemistry shows no change. The urine, in addition to large amounts of blood, shows albumin in variable amounts and all kinds of casts. The urinary output remains normal.

The prognosis is always good and even when hematuria has been present for several months, renal function tests have remained normal. The condition is, therefore, a benign one, although Volhard thinks that if unrecognized, sufficient glomerular change may occur to produce a chronic diffuse nephritis. The course is usually short, but hematuria may be present for months.

(B) Severe Diffuse Glomerulitis.—The clinical features of this type of nephritis are definite. The onset is preceded by an acute infection, usually sore-throat, fever and malaise. After an interval of a few days or a week during which the child may appear to have recovered, the urine is noticed to be smoky or bloody and scanty. The mother may notice that the eyes are puffy. Or there may be nausea, vomiting, and visual disturbances. Blackfan notes that the edema in this type may be very slight, and that it is a hard tense edema that

does not "pit." A moderate but usually definite increase in blood-pressure goes with this type. Uremia is not uncommon.

The urine is bloody, of high specific gravity (1.020 to 1.030), and the total output is much reduced, sometimes to complete anuria; albu-

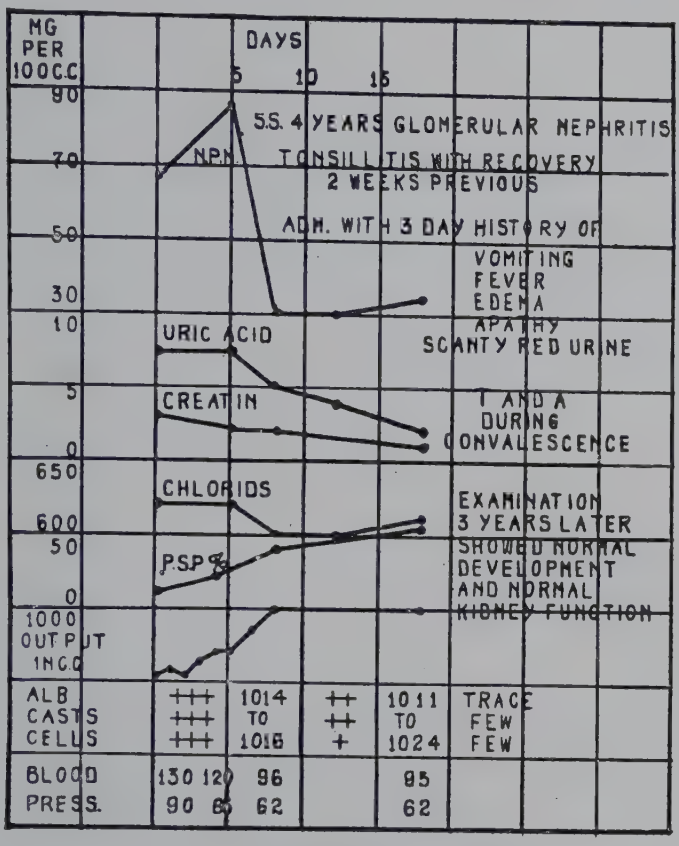


Fig. 17.—Acute Glomerular Nephritis.

min is present in variable amounts, sometimes as much as in the tubular form of nephritis.

The sediment contains red blood-cells with many pus and epithelial cells. A transient pyuria is quite common. All variations of casts are seen, but there are large numbers of casts with red blood-cells attached to them or in which orange-colored masses can be seen. According to Addis these casts are pathognomonic of this type of nephritis.

When the infection (tonsillitis, scarlet fever) which has caused the nephritis has run its course and normal conditions in the kidney have

been restored, the urinary picture changes accordingly. In untreated or improperly treated cases, or when the infection persists, the urine will continue to show the activity of the infection by the presence of increasing amounts of albumin, cells and casts. Frequently it is only when the focus of infection is found and removed or treated that the urine returns to normal.

Kidney Function.—It is possible to have acute glomerulonephritis in children with, so far as we are able to tell, normal kidney function, but it is not usual.

Phthalein output is usually markedly reduced, 0 to 5 per cent in two hours. Occasionally low normal (30 to 40 per cent) values are reported.

It is difficult to get two-hour tests on infants and children. Those that we have been able to get give variable results. Sometimes there has been a normal variation in specific gravity and in amounts of urine passed. In some cases we have found a fixation at a medium level, 1.020 to 1.024. Except in older children, results are not satisfactory.

Blood Chemistry.—Here again, it is quite possible to have clinical and urinary evidence of a severe nephritis without much change in the blood-picture.

There is usually a moderate to a severe degree of nitrogen retention, the N.P.N. ranging from 40 to 100 milligrams or more per 100 c.c. of blood; uric acid from 4 to 16 milligrams; creatinin from 2 to 4 milligrams or more. With diuresis and clinical improvement there is a quick return to normal of all the nitrogenous metabolites. Except in a general way, there is not much help from a prognostic standpoint, to be got from these determinations. Occasionally in acute nephritis and kidney conditions (stone, reflex anuria) a creatinin higher than 5 milligrams is observed. This does not carry the grave prognostic significance that the same finding would in a case of chronic nephritis. Frequently in acute conditions figures as high as 10 to 15 milligrams have been reported with recovery. They do afford one index of the severity of the condition, but cases with extreme nitrogen retention get well just as often and as promptly as those without. A creatinin above 5 milligrams in acute nephritis does not necessarily mean a fatal outcome. It should mean a guarded prognosis.

The acid-base balance is sometimes disturbed in this form of neph-

ritis, but it is not a constant finding. Low or normal values for plasma bicarbonate are found. At the onset there is a mild ketosis which may become more marked. This may be due to vomiting, starvation, or infection, and is not part of the nephritis. Chlorids are low or high, and Blackfan believes that in a few of his cases acidosis was due to an increased concentration of the chloridion.

The sugar content is normal and the cholesterol is either normal or high normal. High cholesterol indicates a tubular element.

The serum and plasma protein are normal and the relation between the albumin and globulin is normal. The fibrinogen is not increased.

In severe acute glomerulonephritis, uremia is a not uncommon occurrence. In Blackfan's series it occurred in 11 of 24 cases. Blackfan finds that steady increase in arterial tension and an increase in edema are the most reliable signs of approaching uremia. Lumbar puncture gives fluid under increased pressure, and he thinks that intracranial tension resulting from edema of the brain is the cause of cerebral symptoms in this form of uremia. Examination of the blood and urine gives no reliable information as to the onset of uremia. Oliguria, anuria, and nitrogen retention are almost the rule in this condition, but it is a mistake to think that the severity of the condition is dependent on these findings.

The course is usually short, two to six or eight weeks, if uremia does not develop. When the hematuria and albuminuria persist with casts and cells, and with or without good kidney function, it usually means that an infection is keeping the process active.

In general, it may be said that the immediate prognosis in acute glomerular nephritis is good. There is very little accurate information as to the intermediate and late prognosis. In some series of cases less than 10 per cent of the series examined fifteen to twenty years after an attack of glomerular nephritis were found to have evidence of nephritis. Other workers think that while a focal glomerulitis can be cured, a severe diffuse glomerulitis is never cured, and that a great deal of the chronic nephritis of adults can be traced directly to a previous attack of glomerular nephritis.

2. *Acute Tubular (Parenchymatous) Nephritis.*—The clinical features of this type of nephritis (nephrosis) are quite different from those in the preceding type. In most of the cases the onset is insidious,

and there is no history of an acute infection before the illness. But some of these cases do follow an acute infection and this type of acute nephritis may accompany, though not commonly, scarlet fever, diph-

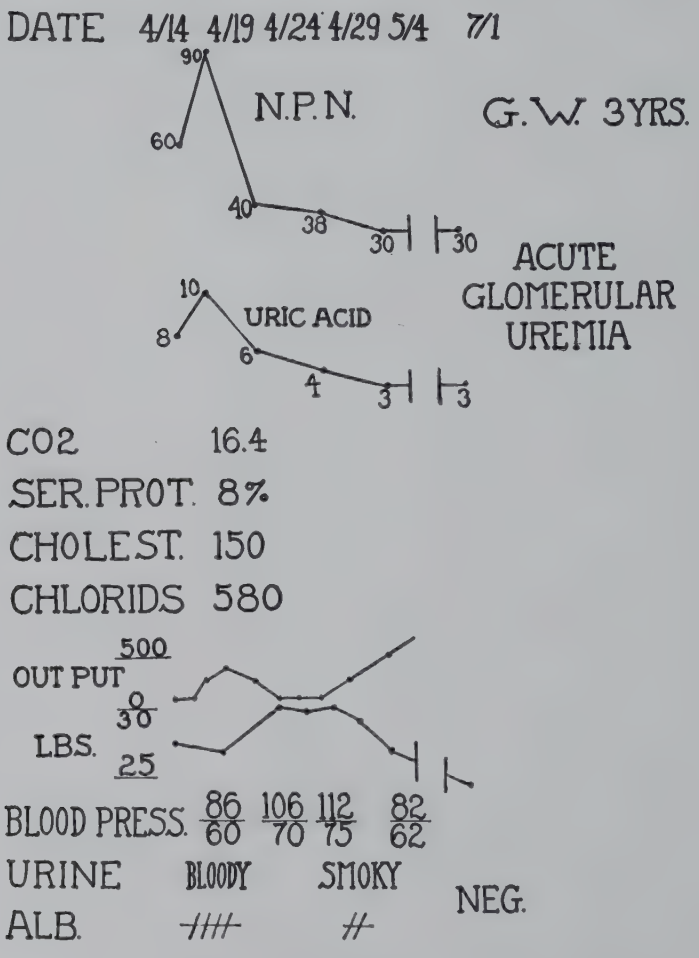


Fig. 18.—Acute Glomerular Nephritis with Uremia.

G. W., 3 years old. Onset with hematuria, but no edema, 3 weeks after tonsillitis. Uremia developed with a rise in the blood-pressure, increase in edema and decrease in urinary output. The non-protein nitrogen was normal during the uremic attack.

theria, typhoid fever or pneumonia. Albuminuria may be the only indication of renal dysfunction or edema may be the first symptom, and it is usually marked and extensive. Oliguria is marked. Occasionally there is fever, but visual disturbances and vomiting are not common.

There is no rise in blood-pressure. Uremia is rare and recurrence is common.

The urine in this type of nephritis is yellow and of high specific gravity (1.020 to 1.050). The gravity is usually much higher than

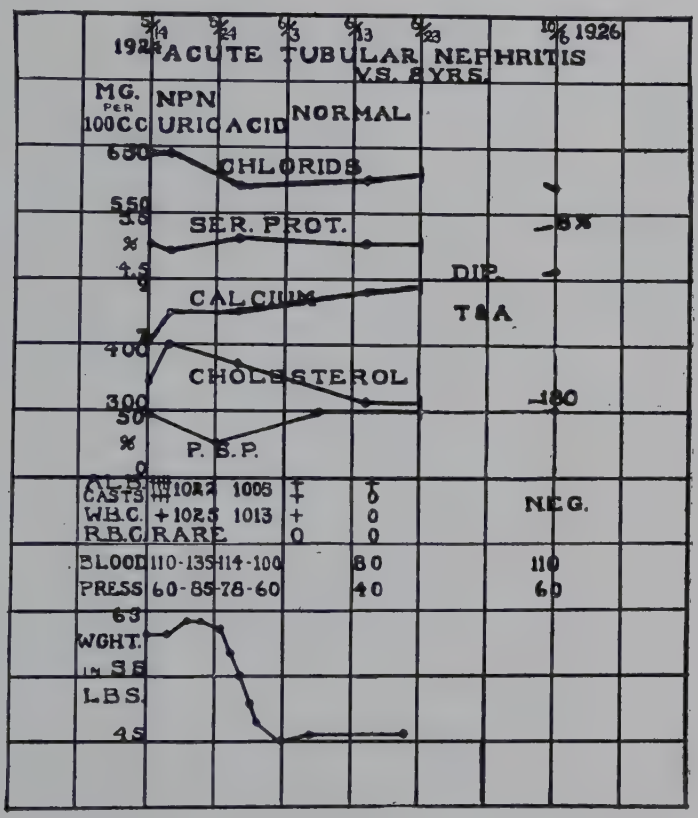


Fig. 19.—Acute Parenchymatous Nephritis.

An eight-year-old boy in his second attack of edema and albuminuria. This case is predominantly tubular; that there might have been some glomerular damage is shown by the presence of a few red cells and by a high blood-pressure on one occasion.

in the acute glomerular form. The total output of urine in twenty-four hours is much diminished, sometimes less than 100 c.c. being passed, and rarely there is almost complete anuria. Albumin is the outstanding feature in this type, the urine frequently boils solid, and quantitatively up to 10 grams per liter are found.

The sediment contains many fine hyaline, granular, waxy casts

and doubly refractile lipoid granules. Leukocytes and epithelial cells are seen, but there are few or no red cells.

The phthalein output may be moderately low but is usually normal, and the two-hour test may show a fixation of specific gravity at a high level, or a normal variation.

Changes in the blood are characteristic. Early there may be a moderate degree of nitrogen retention, the figures for N.P.N. and uric acid being high, normal or slightly above normal.

The chlorids may be normal or high, 600 to 650 milligrams per 100 c.c., the cholesterol is high, up to 900 milligrams per 100 c.c., and lipemia is common. High cholesterol values are not found in other types of nephritis.

The protein content of the serum is low. Instead of a normal protein of 6.5 to 8 per cent figures as low as 3.6 per cent are found. The relation between the albumin and the globulin fractions is changed. The normal relation is albumin 4.5 to 6.5 per cent, with globulin 1.5 to 2.5 per cent. In this type of nephritis there is a reduction in the albumin fraction (sometimes lower than 1 per cent) while the globulin fraction is normal or slightly increased. The fibrinogen is increased. Instead of the normal 0.2 or 0.25 per cent values of eight or nine times normal may be found.

With the drop in serum protein due to albumin loss in the urine and edema fluid, there is a fall in the serum calcium. Normally the calcium in the serum is from 9 to 11 milligrams per 100 c.c. and this is quite constant. In this type of nephritis the values for calcium are commonly cut in half, depending of course on the amount of protein lost. Since it is the un-ionized calcium that is bound up with the protein molecule, the drop in calcium causes no symptoms of tetany. Another factor that influences the calcium level is the phosphate content.

High values for inorganic phosphate are commonly found in this type of nephritis. Instead of the normal 4 to 5 milligrams per 100 c.c. of blood, values as high as 8 to 12 milligrams are found.

Variations in the basal metabolic ratio are difficult to determine in young children. Low rates are found in some cases and on this basis, Epstein recommends thyroid treatment. Murphy and Warfield say that, "as a matter of fact, all cases do not have low basal metabolic rates. Further, can one say that in a patient whose tissues are edema-

tous, and whose weight is therefore a matter of estimation, that a —10 or —15 rate means hypothyroidism? We doubt whether that is a justifiable conclusion. Even the patient who has lost his edema is still ill and usually undernourished, so that a rate around —10 or —15 would not be unusual."

Changes in the acid-base equilibrium are not constant. A mild or occasionally a moderately severe ketosis is present in young children and infants with a corresponding drop in the bicarbonate, but a real acidosis due to failure of the kidney to maintain acid-base equilibrium is rare. Blood volume is normal according to Elwyn.

Murphy and Warfield think that pure nephrosis is rare, although undoubted cases have been reported. Most of the acute cases tend to go over to the chronic condition, and in our experience, at some time in the course of the disease, evidences of acute glomerulonephritis (red cells in the urine, increase in blood-pressure, nitrogen retention) will appear if the cases are closely watched. It is, of course, always possible to have an acute nephritis superimposed on a nephrotic basis, or a nephrosis on a nephritic basis. Murphy and Warfield point out that if one grasps this conception it simplifies, to some extent, the chaos into which kidney disease has been brought.

Laboratory work will not be of much help in prognosis. It does serve as an index of the severity and progress of the condition, and will give certain indications for treatment. With low serum protein and no nitrogen retention, a high protein diet should certainly be given. Peters has called attention to a degree of protein starvation in these cases. With high plasma chlorids, one is justified in restricting salt intake.

This type of nephritis tends to run a chronic course, the history being one of repeated attacks of edema and albuminuria, regardless of the treatment employed. If they survive the infection (pneumonia, peritonitis, erysipelas) to which they are so susceptible, a fair proportion of them get well eventually, but it usually is a question of years.

A certain number of these cases go over into a chronic diffuse glomerulonephritis. These will be discussed later.

3. *Acute Mixed Glomerulotubular Nephritis.*—These cases show the clinical features and laboratory findings of the other two types. If in a case showing hematuria, nitrogen retention and increased blood-

W. H. 4 YRS.
ACUTE DIFFUSE

DATE	6/1	7/1	8/2	9/22	10/10
N.P.N.	40	30	20	29	29
SER. PROT.	3.8%	4%	4.6%	3.9%	4.7%
CHLORIDS	525	580	585	597	573
CHOLEST.	565	317	727	800	890
URINE	YELLOW	"	"	"	BLOODY
ALB.	###	###	1%	1%	1%
R.B.C.	FEW	"	"	"	###
BLOOD PRESS.	100/75		110/70	112/70	100/70

Fig. 20.—Acute Mixed Glomerulotubular Nephritis.

It is predominantly tubular as shown by the very high cholesterol and very low serum protein and the massive edema present. That there was some glomerular damage is shown by the presence of gross hematuria on several occasions, and a systolic blood-pressure well above 100 mm. Hg most of the time.

C. W. 11 YRS.
ACUTE DIFFUSE

DATE	5/26/27	6/8	6/30	7/20	8/30	9/15	10/15
N.P.N	55	53	40	40	28	22	25
SER. PROT.	5.3%	6%	7%	6%	6.7%	5.7%	
CHLORIDS	644	597	585	620	620	590	573
CHOLEST.	444	470	380	300	200	246	271
URINE	BLOODY						
ALB.	.9%		.6%	.6%	.4%	.5%	.4%
BLOOD PRESS.	144/100	134/82	108/66	120/90	110/70	90/60	110/80
WEIGHT	89	73	71		68	68	70	70

Fig. 21.—Acute Mixed Glomerulotubular Nephritis.

Predominantly glomerular as shown by a persistent nitrogen retention, persistent gross hematuria and hypertension. Some tubular involvement evidenced by the massive edema and high cholesterol, although the serum protein was never very low.

pressure, we have a massive edema and albuminuria with low serum protein, high chlorids and cholesterol, we are justified in making a diagnosis of a mixed lesion. Either type may predominate.

Complete recovery may occur in this type, but the prognosis is not good. They tend to run a chronic course with one or the other element predominating at different times.

The laboratory findings are a combination of those found in the two types and they vary with the severity and persistence of the kidney damage.

The essential laboratory findings in the two common types of nephritis are given in the table.

	Glomerular	Tubular
BLOOD CHEMISTRY		
Nitrogen retention	Normal or + to ++	None
Serum protein	Normal	Low
Albumin	Normal	Low
Globulin	Normal	Increased
Chlorids	Normal	Increased
Cholesterol	Normal	Increased
URINE		
Character	Bloody	Yellow
Specific gravity	Normal	High
Albumin	+ to ++++	Massive
Microscopic	Blood-casts	Hyaline casts
	White blood-cells	White blood-cells
	Red blood-cells	No red blood-cells or rare
Phenolsulphonephthalein	Normal or low	Normal or high

Bacteriology of Acute Nephritis.—Most of the acute glomerular, diffuse and tubular nephritis is preceded or accompanied by an acute infection. The accompanying table emphasizes the rarity of the absence of infection in acute nephritis.

Recent Infection in Acute Nephritis

	Glomerular	Diffuse	Tubular
Total cases	74	17	8
Upper respiratory tract	50	8	5
Pneumonia	17	3	1
Miscellaneous	3	2	0
No history of infection	4	4	2

Ninety-five per cent of the glomerular, 77 per cent of the diffuse, 75 per cent of the tubular gave a definite history of recent infection. These figures are borne out by other workers. Blackfan reports an antecedent infection in 83 per cent of his cases, and Longcope in 85 per cent.

In the glomerular type of nephritis the hemolytic streptococcus is the most common offender. It is recovered only occasionally from the urine, but almost invariably from the foci, tonsils, teeth, sinus, ears, etc. In tubular nephritis a staphylococcal infection is said by some workers to be the exciting agent, and others report that this type of case occurs frequently without any antecedent infection. It is well known, however, that they are very susceptible to infection, and the cause of death in most of them is an overwhelming pneumococcus or streptococcus infection, usually a peritonitis. In those cases of glomerular nephritis that persist or become chronic, it is almost the rule to find a focus of infection somewhere which is harboring a hemolytic streptococcus. The tendency for tubular nephritis to become chronic irrespective of infection is well known.

It is not thought that the nephritis is actually caused by the presence of organisms in the kidney. Blood- and urine-cultures are usually sterile. Longcope suggests that the "toxins" liberated by the growth of streptococci and eliminated through the kidney may cause nephritis in patients rendered highly susceptible in some way to these toxins. In other words it is a form of allergy.

Prognosis.—One might think that with all the elaborate laboratory work and kidney function tests we would be in a better position to predict the outcome in acute nephritis. But the laboratory work together with the history and physical examination are of little value in trying to get at the prognosis. Those cases in which the clinical and laboratory findings point to a severe degree of nephritis take a little longer to convalesce, but have no greater tendency to become chronic than those cases with a mild nephritis. What does seem to play a rôle in the production of chronic nephritis is the persistence or recurrence of infection. Longcope reports that "12 cases among those that could be constantly observed, progressed to a chronic state or terminated fatally. In 10 of these, or 83 per cent, the infection or infecting organism has persisted." In a series of cases that we have had under

observation, 8 of 9 cases that became chronic had a careful follow-up. Six, or 75 per cent, of these had persistent or recurrent infection.

Other Forms of Acute Nephritis.—While the bulk of nephritis seen in infancy and childhood comes under the above classifications other types are met with. The most common are purulent nephritis and luetic nephritis. Purulent nephritis will be discussed under pyuria.

Luetic nephritis is perhaps more common than most clinicians realize. Compos, in a pathological study of 69 cases of congenital lues, found histologic changes in the interstitial or parenchymatous tissue in every case. Parenchymatous changes were more marked in those infants who had an extra-uterine life. Other workers report the same changes. Clinically, it is difficult to prove that a nephritis occurring in the course of syphilis is due to syphilis. Yet in a young infant with the stigma of lues, a positive Wassermann and nephritis that is the most likely diagnosis. Infectious nephritis is rare under two years of age. The prognosis is bad and treatment should be forced in spite of the nephritis.

All types of nephritis are met with, and the blood chemistry changes depend on the type and extent of the lesions.

In the cases we have seen there has been very little change in the blood chemistry. Nitrogen or chlorid retention is not marked. A high cholesterol is noted occasionally, and some of the cases show a low serum protein with a reversal of the albumin globular ratio. Blood chemistry findings in a three-month-old infant with syphilis and nephritis:

Date	Milligrams per 100 c.c.					Serum Protein, Per Cent
	N. P. N.	Chlorid	Cholesterol	Phosphate	Calcium	
Nov. 1.....	38	597	243	3.9	10.0	7.2
Nov. 24.....	29	585	163	4.3	10.3	7.6
Dec. 9.....	26	585	145			7.8
Feb. 3.....	35	562	167			7.5

The urine at first was hemorrhagic, had four-plus albumin with many hyaline and granular casts. The urine returned to normal after intensive treatment, but the child died of intercurrent infection after four months' observation. Autopsy showed a moderate degree of tubular degeneration.

Chronic Nephritis.—Chronic nephritis is relatively rare in childhood. In the Pediatric Division at Bellevue Hospital in the course of seven years 150 cases of acute nephritis were observed as compared to 15 cases of chronic nephritis. We think though, that if more routine urinalysis were done whether there was any "indication" for it or not, and if the blood-pressure apparatus were used more frequently by practitioners and pediatricians, more cases of chronic nephritis in children would be discovered.

Classification of chronic nephritis is difficult. That proposed by Addis is simple and satisfactory, and will be followed here. We must remember that nephritis is always more than a disease of the kidney, and that we can have two or three pathological processes going on at the same time in the same kidney. It must also be borne in mind that quite different clinical and laboratory pictures are found in the initial, active, quiescent and terminal stages of one type of chronic nephritis. To further complicate the situation any type of acute nephritis can be, and frequently is, superimposed on any type of chronic nephritis.

1. *Chronic Glomerular Nephritis.*—The first stage of this type of nephritis has been dealt with under acute nephritis. According to Addis this initial process can go to a latent or active stage over a period of years, and from either of these stages can go to healing or the terminal stage. This is probably determined by the continuance or the disappearance of the infection to which the process is due.

Kidney function in the *latent stage* is normal. Blood chemistry is normal, functional tests give normal results, and the only indication of trouble is found in the urine. Even this may be passed as normal unless a concentrated urine is examined. Addis employing his method of counting cells and casts reports that cases in this stage always have an abnormally high number of red blood-cells and blood-casts.

The *active stage* following upon the initial attack or a latent period shows a variable clinical and laboratory picture depending on the type and extent of the kidney damage. It may give in a mild form the same findings we get in the acute glomerular nephritis. The urine contains variable amounts of albumin, gross or microscopic hematuria with bloody, hyaline and granular casts. There may be some impairment in the ability to excrete phthalein and there may be a tendency to fixation of specific gravity at a medium level. Blood chemistry is normal or

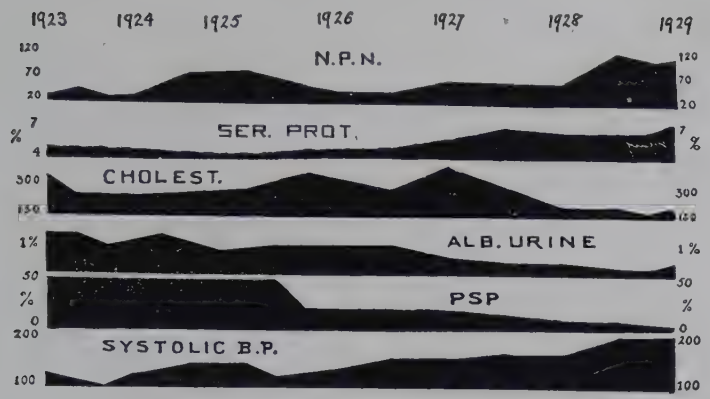


FIG. 22.—CHRONIC GLOMERULAR NEPHRITIS.

M. G., male, 11½ years old, white.

Past History.—Scarlet fever at 1 year, no complications. Measles and whooping-cough at the age of 5, chickenpox and mumps at 6 and 7 years. Frequent sore-throats. Pneumonia at 6 years, at 7 years, and finally at 11 years, 3 weeks before the onset of nephritis.

Present History.—In December, 1923, 3 weeks after an attack of pneumonia, a generalized edema was noticed. There was a massive albuminuria and cylindruria but no hematuria, elevation of blood-pressure and nitrogen retention at onset. In February, 1924, he developed an acute ethmoiditis with hematuria, moderate nitrogen retention and a rise in blood-pressure.

Course.—The history for the past 5½ years is one of repeated infections, chronic pansinusitis, pneumonia, bronchitis and laryngitis, recurrent edema and albuminuria with exacerbations of acute glomerular nephritis. Hemolytic streptococci were occasionally recovered from the throat and the sinus washings. There was a persistent rise in the nitrogen retention and a steady rise in blood-pressure, as well as a drop in phthalein excretion to zero. The nephrotic manifestations have almost disappeared; the serum protein has gone up from 4.2 to 6.5; the cholesterol decreased from a high level of 380 to 190 milligrams, and the albuminuria, while marked, varies from 0.2 to 0.3 to a high reading of 2.5. The specific gravity of the urine formerly fixed at a high level, now fixes at a low level. The edema has practically disappeared.

Summary.—A boy 11 years of age develops an acute tubular nephritis following a pneumonia. Early in the course the nephrotic manifestations were marked, but his repeated infections have given him more and more glomerular damage, as shown by hematuria, elevation of blood-pressure and nitrogen retention.

Shortly after this chart was finished he became much worse, eye-ground changes became marked, blood-pressure came down, extreme anemia developed; there was a severe grade of acidosis and azotemia with death in uremia 6 years after the onset.

Autopsy not permitted. *Diagnosis:* Chronic glomerulotubular nephritis.

shows a moderate degree of nitrogen retention. In many of the cases tubular degeneration is likely to occur. This gives the picture we associate with nephrosis. There is an increase in the edema, albuminuria is marked, in addition to hyaline casts, fatty casts are present as well as doubly refractile lipoid bodies. Red cells and blood-casts are diminished, but present. The blood chemistry, in addition to a moderate

degree of nitrogen retention, shows a marked reduction in serum protein at the expense of the albumin fraction, high chlorids and high cholesterol. Calcium is usually low and phosphate high. Secondary anemia is usually present.

Whether from the active stage the nephritis goes on to the terminal stage or becomes healed depends on presence of infection, and the ability of the patient to overcome it.

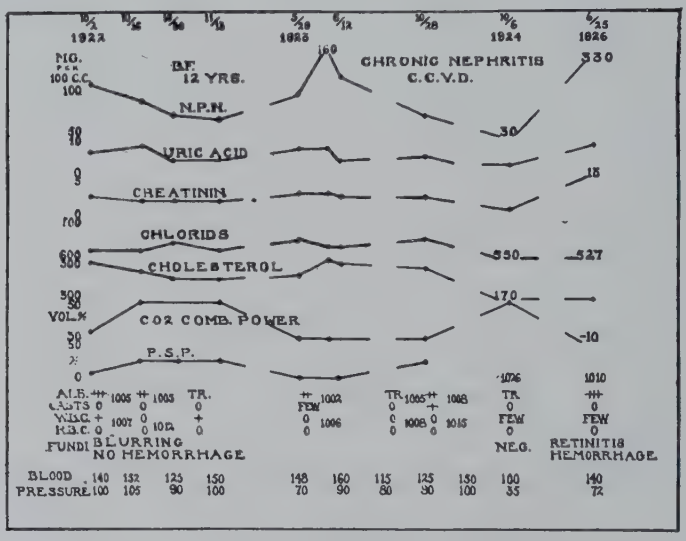


Fig. 23.—Chronic Glomerular Nephritis.

This case was complicated by chronic cardiac valvular disease. No edema at any time. There was a remission of all nephritic symptoms and findings for about two years. Later the picture was that of chronic interstitial nephritis, and terminal uremia occurred four years after onset. Autopsy showed a contracted kidney.

The pathological change in the terminal stage is one of fibrosis, and the clinical, and laboratory picture changes accordingly. As more and more units are disabled and fibrosed, signs of kidney insufficiency become more marked. Nitrogen retention increases and the urinary picture changes. Red and white cells disappear and only traces of albumin are found. The phthalein excretion drops to zero, and since only a dilute urine can be put out there is a fixation of specific gravity at a low level. The acidosis that sometimes develops will be dealt with later.

2. *Degenerative Nephritis.*—This is a convenient term to include many forms of nephritis, the predominant pathology of which is renal

degeneration in contrast to the inflammatory and sclerotic forms of nephritis.

What was said in the introduction to chronic nephritis regarding the variety of pathology possible in one kidney, the various stages of the disease and the acute element added to any chronic process applies here.

In adults the condition is met with in pregnancy and in poisoning with mercury, chromium, and uranium salts. These conditions are not seen in childhood.

The question of nephrosis comes up to confuse an already complicated situation. No attempt can be made to discuss it in detail here. Müller, a number of years ago, used the term nephrosis to separate those cases in which degeneration was the feature from those cases in which inflammatory changes were marked. The important features of nephrosis are as follows: Clinically, there is an insidious onset without obvious infection preceding, massive edema, and normal blood-pressure and fundi. The urine shows a massive albuminuria, oliguria, high specific gravity, hyaline casts and doubly refractile lipoid bodies, but no red blood-cells. Phthalein secretion is normal. The blood chemistry shows no nitrogen retention, a low serum protein at the expense of the albumin fraction and a high cholesterol. The basal metabolism is low. Anatomically, extensive fatty degeneration of the tubules is found with intact glomeruli. The course is chronic though cure is possible. The prognosis is bad because of the peculiar susceptibility of these patients to infection, especially pneumococcus. According to Epstein who calls the condition diabetes albuminuricus, this is not nephritis at all. It is a perversion of protein and fat metabolism of which the renal changes are only one manifestation of the underlying metabolic disorder. Epstein thinks it is an endocrine dysfunction with lowered thyroid activity. Changes in the thyroid have been reported in these cases. Other workers use the term loosely to apply to various forms of nephritis where degeneration is a prominent feature, such as sublimate nephrosis, febrile nephrosis, lipoid nephrosis, syphilitic nephrosis, amyloid kidney, and chronic glomerular nephritis with degenerative changes predominant.

The anatomical evidence for a pure nephrosis is scanty. Christian, in a large experience with chronic nephritis, has had but one autopsy

that showed the renal changes consistent with nephrosis; tubular degeneration without glomerular lesions, and that patient did not show the clinical picture of nephrosis. Baehr at the Mt. Sinai Hospital has only once seen a pure nephrosis in an adult at autopsy and that was in a syphilitic. Baehr also thinks that pure nephrosis is not infrequent in children. In our experience at Bellevue, it is a rare occurrence. The cases that show these features if watched carefully and long enough will always show some clinical evidence of glomerular injury, hematuria, hypertension or nitrogen retention. We have seen only one case where the clinical and anatomical evidence would permit a diagnosis of pure nephrosis.

Degenerative nephritis is met with in children in the following conditions:

Infection.—(*a*) Any generalized infection can produce cloudy swelling associated with slight glomerular damage. (*b*) Focal infection frequently is associated with this type of chronic nephritis. (*c*) Osteomyelitis with sinus formation or any chronic infection frequently leads to the waxy or amyloid kidney. (*d*) Lues.

Cryptic.—When no cause for the condition can be found.

The essential laboratory findings are those we have outlined under tubular nephritis and in the discussion of nephrosis. Variations from these findings are due to acute infections which these cases are so susceptible to, or to acute nephritis engrafted on the chronic condition. These cases may have long latent periods and go on to complete recovery, or progress until an intercurrent infection (pneumococcus or streptococcus) ends the picture with or without uremia.

3. *Arteriosclerotic Nephritis.*—This type of nephritis (chronic interstitial nephritis or nephrosclerosis) so common in adults is rare in children. When it does occur the clinical and laboratory findings are the same as in the adult type.

Clinically it is characterized by hypertension with palpable peripheral vessels, cardiac hypertrophy, retinal changes, and absence of edema.

The laboratory findings in a well-developed case are characteristic. There is a polyuria with a fixation of gravity at a low level. Merely traces of albumin are found with a few hyaline casts, and occasional red or white cells. Phthalein excretion is low.

Blood chemistry shows a marked degree of nitrogen retention with N.P.N. up to 400 milligrams, uric acid up to 20 milligrams. A creatinin of above 5 milligrams in chronic nephritis makes a definitely bad prognosis. There is little or no change in serum protein or cholesterol. Chlorids may be normal or high. The changes that occur with acidosis will be discussed later.

In early cases of this type of nephritis where kidney function is apparently good, the laboratory is of some help in making a diagnosis. There is no nitrogen retention early, but there is a loss of the ability to concentrate nitrogen waste, and urea is kept at a normal level by the ability of the kidney to keep up a polyuria. The normal kidney can concentrate waste products in any required amount, whereas the damaged kidney has lost this elasticity and puts out the same amount of waste in a larger amount of urine that is in less concentration. Various tests have been devised to put this in a mathematical formula, Ambord's coefficient, Addis' ratio and Van Slyke's clearance test. This last takes into account more variables, and is within limits one of the best kidney function tests we have.

The etiology of these conditions in children as in adults is not well known. In several of the severe cases of this type that we have seen, there has been associated a chronic renal infection on an obstructive basis.

Renal Rickets (Renal Infantilism; Renal Dwarfism).—This interesting condition has only recently been carefully described. Hunt in this country collected 42 cases, Park and Shipley have described the bone changes. Parsons and Paterson in England have written about it. It is curious that the early accounts and most of the recent work have come from England.

Clinically, the first signs are associated with the nephritis. Often the only symptoms of the nephritis are polyuria and polydipsia which may be present from birth. Edema, hypertension, retinitis, cardiac hypertrophy are not always present. At autopsy the kidneys are small and show a severe grade of chronic interstitial nephritis.

Clinical rickets may be present, beading of the ribs, large epiphyses and genu valgum. Hess states that "interesting and at times characteristic changes have been noted in the bones by means of the Roentgen rays."

These children show a definite stunting in growth and there may be infantilism. Uremia terminates the picture, usually before puberty.

The following laboratory findings taken from a case recently seen at the Babies' Hospital show the characteristic changes found in these cases:

Kahn Test: Negative.

Blood Chemistry:

N. P. N.	165- 217 mg. per 100 c.c.
Creatinin	12-15.4 mg. per 100 c.c.
Serum protein	7.4- 8.7 per cent
Sugar	166- 187 mg. per 100 c.c.
Chlorids	575- 475 mg. per 100 c.c.
Cholesterol	146- 186 mg. per 100 c.c.
Calcium	8.5-8.9, 7.6, 8.2 mg. per 100 c.c.
Phosphate	9.8, 10.4, 12.0 mg. per 100 c.c.
Carbon dioxid combining power	18,-16,-10 volume per cent

Hemoglobin 42 per cent red cells 2.2 white cells 17,000, 94 per cent polymorphonuclears

Urine:

Lemon yellow, turbid, albumin 0.1 to 0.2 per cent, few white cells, rare red cells, culture sterile, phenolsulphonephthalein zero, specific gravity fixed below 1.010.

Uremia.—Volhard and Fahr described two types of uremia. One they called eclamptic pseudo-uremia. This is the type that occurs in eclampsia and in acute glomerular nephritis, and has been discussed under that subject. Volhard and Fahr, Blackfan and others believe the symptoms to be due to increased intracranial pressure associated with hypertension and edema. The prognosis in this type is relatively good and it is important to distinguish the two types.

True uremia is usually the end picture of chronic interstitial nephritis. Clinically it is characterized by wasting, gastro-intestinal disturbances, infection, convulsions and twitching, coma and death from cardiac failure. It is not always stormy but may take the course of the so-called latent uremia such as occurs when the only kidney is accidentally removed. Visual disturbances or attacks of vomiting, lassitude and weakness may be the only symptoms shortly before uremia develops.

Blood chemistry gives a reliable index of the approach of this condition. We cannot go into all the complex questions of chemistry involved in these changes. It is not thought that the excess or decrease in the blood constituents has any direct relation to the causation of uremia. The changes may explain certain symptoms. For the clinician the chief value of blood analysis is in diagnosis and prognosis.

There is an extreme degree of nitrogen retention, due to a proportionate rise in all the nitrogenous metabolites, N.P.N., urea, uric acid and creatinin. According to Foster this indicates the last stages of renal insufficiency. This is accompanied by a low chlorid, calcium, and a marked lowering of the alkaline reserve. There is also an accumulation of phosphates and sulphates.

Polycystic Kidneys.—The clinical diagnosis of this condition is seldom made. While rare it is probably more common than we formerly supposed. Garceau in the Boston City Hospital found 10 cases in 2429 autopsies. In a newborn infant with a large abdomen and masses in the flanks the condition may be suspected, but cannot be differentiated from kidney tumor and hydronephrosis. While the condition is probably congenital and an hereditary tendency has been observed, there may be no symptoms for many years. If infection or nephritis does not occur, and if enough good kidney tissue is left between the cysts, clinical and laboratory data will be negative. Pain, hematuria, and the presence of a bilateral tumor are usually the first signs, but frequently cases do not present themselves until in the last stages of renal insufficiency.

In the early stages the urine and blood may show no changes and kidney function tests will be normal. If infection takes place the condition may be thought to be an ordinary pyelitis. Later the picture is that of interstitial nephritis with high blood-pressure, polyuria, azotemia, and eye-ground changes with uremia and death. There is no treatment for this condition.

Cystoscopy and pyelography may help in the early diagnosis where the condition is suspected.

An unusual type of polycystic kidney has been described where instead of the large cystic kidneys commonly described, small hypoplastic kidneys are seen with multiple small cysts. At times the cysts

can hardly be seen with the naked eye. The findings and course are not different from the other type of polycystic kidney. Hypoplastic kidneys are frequently the seat of cystic degeneration.

Outline of Work-up for Cases of Nephritis.—The following outline has been found useful in collecting data on a series of cases in hospital practice.

History.—Family History.—For Bright's disease, apoplexy, hypertension, heart trouble, obesity.

Past History.—Protein eating, salt eating, hypersensitiveness, infection—its frequency in the past. The immediate antecedent infection, symptoms referable to the urinary tract, amount of urine, hematuria, previous urinalyses.

Physical Examination.—Careful search for foci of infection, such as teeth, tonsils, sinuses, etc.

Fundi.—To be examined on admission and findings checked by ophthalmologist.

Ear, Nose and Throat Consultation

Blood-Pressure.—All cases of acute glomerular nephritis should have a blood-pressure reading daily during the acute stage. If hypertension is marked or there are cerebral symptoms it should be taken two or three times a day. In chronic nephritis with hypertension make daily observations and in those cases without hypertension make observations weekly or as indicated.

Weight.—Should be ascertained every other day if edema is present; if no edema, weigh weekly.

Complete Blood-Count on admission and discharge.

X-Rays.—Chest, 6 foot plate of heart, sinuses, teeth, and in chronic cases, long bones.

Urological Investigation on all chronic cases with persistent pyuria.

Blood Chemistry to be done on admission and repeated as ordered by an attending physician.

In hospital practice more or less complete blood chemistry is done as a matter of scientific interest. For the man in practice, an N.P.N. or urea N., and if these are elevated, a creatinin determination, serum protein, cholesterol and chlorids will give all the information necessary for diagnosis and treatment.

SEROLOGY

URINE.—A casual specimen for routine examination to be sent to laboratory on admission.

Phenolsulphonephthalein, concentration, dilution and urea clearance tests to be done as soon as possible after admission. These tests are repeated as indicated.

When the functional tests have been completed the twenty-four-hour urine is collected daily. Each voiding is collected separately and sent to the laboratory one or two times a day. The amount need not be measured on the ward since that is done in the laboratory.

BACTERIOLOGY

Blood-culture when indicated
Urine-culture and direct smear
Throat-culture
Culture from any active focus
Stool-culture for streptococci

It is realized that all of these procedures cannot be done on every case, especially young infants. It must also be borne in mind that frequent vein punctures do not make for frequent follow-up visits. Blood for chemistry, culture, Kahn test and urea clearance test can be obtained at the same time. If it is necessary to catheterize for the urea clearance test the same specimen can be used for culture.

Diet and Fluid Intake.—Ordinarily all acute cases should be put on a low protein, salt-poor diet and if much edema is present fluid should be restricted. The diet should be changed and fluid allowed *ad lib.* as soon as kidney function improves. Measure all fluid intake.

Chronic cases with nitrogen retention or low serum protein should be put on a weighed diet as ordered by the intern or attending physician.

DISORDERS IN CARBOHYDRATE METABOLISM

A great deal of work has been done on the blood-sugar in infancy and childhood, and changes in blood-sugar have been reported in a great variety of conditions, some of which will be considered here. All the work done on the carbohydrate metabolism in infancy and childhood seems to indicate less stability than is found in the adult.

Either the carbohydrate reserve of the body is more rapidly depleted, or the infant organism is less efficient in mobilizing glucose suddenly demanded.

The fasting blood-sugar of normal infants with the Myers-Bailey method is 80 to 110 milligrams per 100 c.c., and with the Folin-Wu method is 70 to 100 milligrams per 100 c.c. Low figures in the newborn are common. From a few hours after birth to the fourteenth day there is a rise from 52 to 93 milligrams per 100 c.c. After the first month there seems to be no relation to the age and the blood-sugar level.

Blood-sugar determinations are necessary in the practice of pediatrics in the following conditions: To determine the significance of a glycosuria and to control the treatment of diabetes. They are useful in working out certain endocrine and intestinal disorders.

The clinician who is studying a case of glycosuria must remember that glucose is found in normal urine in amounts so small as will not be shown by Benedict's or Fehling's solution. The urine of normal infants and children contains from 0.05 to 0.1 per cent of sugar.

According to Eagle, glucose is not normally excreted in the urine: "What has heretofore been considered to be glucose, fermentable by yeast, is in reality a group of substances which only gradually decompose under the conditions of fermentation, possibly due to bacterial decomposition. Such decomposition is a matter of days, while the fermentation of glucose is completed in less than an hour. It is these substances which are partially removed by the preliminary shaking of urine with Lloyd's reagent.

"Until a certain critical level of blood-sugar has been reached, the kidney interposes an absolute barrier against the excretion of glucose."

He also found that "by incubating urine at 37 to 38° C. with appropriate quantities of yeast, any glucose present up to 0.4 per cent may be quantitatively fermented within forty minutes. The presence of glucose in concentrations as low as 0.010 per cent may thus be determined, provided certain substances in urine which obscure the results of fermentation are first removed."

In most infants and children, when the blood-sugar reaches 180 milligrams, an appreciable amount of sugar will be put out, enough

to give a reduction of Benedict's solution. Variations in this *threshold* level occur. In renal diabetes glycosuria is present, though the blood-sugar is at a normal level. In certain cases of nephritis and diabetes, blood-sugar may go as high as 200 to 300 milligrams with the urine sugar-free. Therefore, sugar in the urine may result from a lowering of the renal threshold, or may mean a hyperglycemia, and the urine may be sugar-free with a high blood-sugar. Urinalysis alone does not give sufficient information in working up these cases.

Tolerance Tests.—A great variety of tolerance tests are done, and the following is satisfactory for infants and children. The fasting

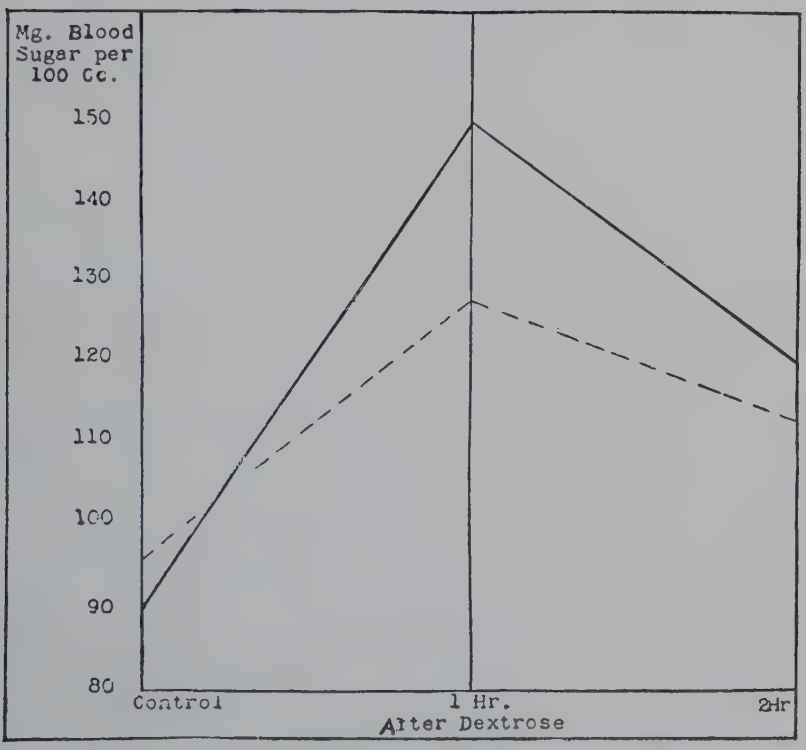


FIG. 24.—A COMPARISON OF THE ALIMENTARY DEXTROSE TOLERANCE OF CHILDREN UNDER 3 YEARS OF AGE (BROKEN LINE), AS COMPARED WITH THAT OF ADULTS (SOLID LINE).

blood-sugar is taken and 1.75 grams of glucose per kilogram of body weight is given in 50 per cent solution. The blood-sugar is estimated one and two hours after. The tolerance of the infant for glucose is greater than that of the adult, and the lag type of curve is frequently

found, *i.e.*, the blood-sugar two hours after the ingestion of glucose is the same or greater than the blood-sugar at the end of one hour. Abnormal curves will be considered later.

It has long been known that hyperglycemia does not develop after

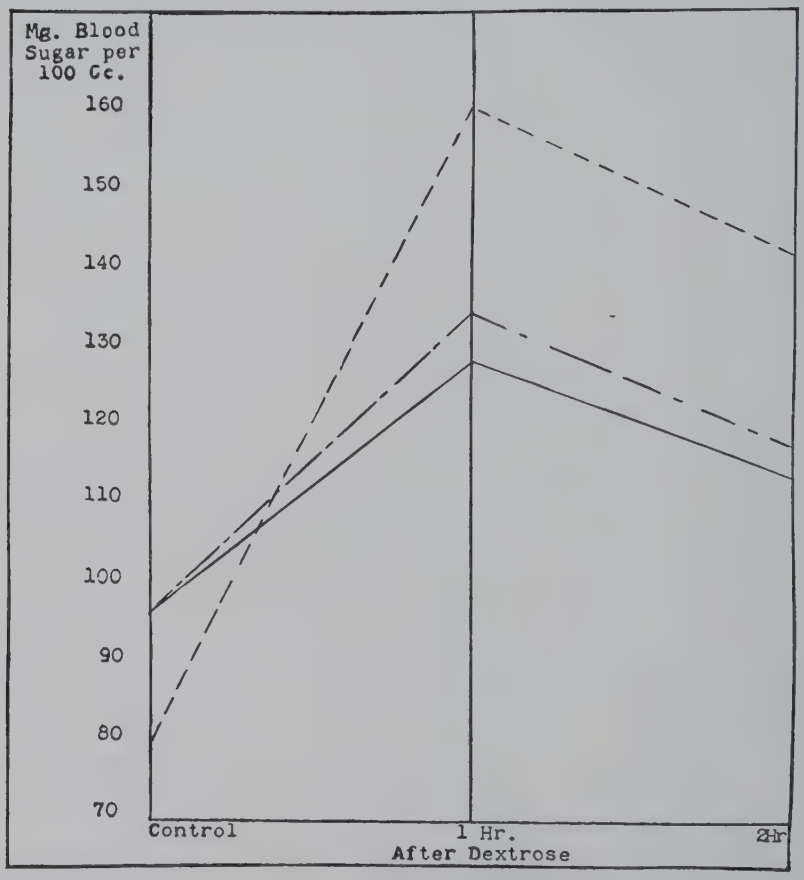


FIG. 25.—A COMPARISON OF THE ALIMENTARY DEXTROSE TOLERANCE OF MARASMIC CHILDREN (BROKEN LINE) AND OF UNDERNOURISHED CHILDREN (DOT-DASH LINE), AS COMPARED WITH THAT OF NORMAL CHILDREN (SOLID LINE).

the ingestion of levulose. This is a slight rise (20 to 30 milligrams) in the blood-sugar, and it is thought that the explanation lies in the fact that levulose is completely removed by the liver. In those cases in which there is clinical evidence of hepatic insufficiency, there is a marked rise in the blood-sugar following the ingestion of levulose.

This test is apparently one for liver function, but its clinical value has not been thoroughly established.

Blood-Sugar in Disease.—*Infection.*—In children with acute infection a hyperglycemia is found occasionally and most of them show an increased tolerance. Tallerman, in 12 cases of infection in chil-

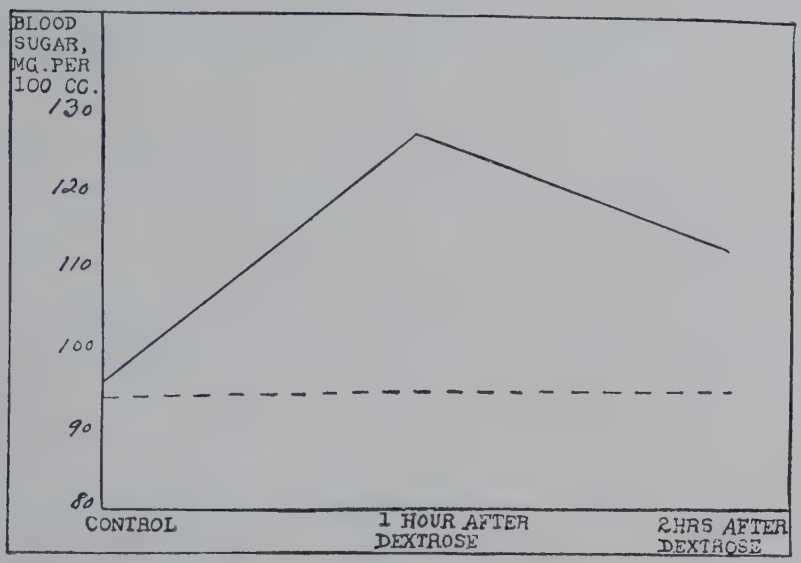


FIG. 26.—ALIMENTARY DEXTROSE TOLERANCE OF PATIENTS WITH CELIAC DISEASE.

1.75 gms. of dextrose in 50 per cent solution was given per kilogram of body weight. The broken line indicates patients with celiac disease and the solid line, normal infants.

dren, found that the fructose tolerance test gave abnormal curves in 9, showing hepatic insufficiency.

Marasmus.—Most workers agree that the blood-sugar level during fasting is low in infants and children markedly underweight for any cause. Values as low as 70 to 80 milligrams are the rule, and as the nutrition improves there is a steady rise in the blood-sugar level. The glucose tolerance test shows a decreased tolerance. The average blood-sugar one hour after ingestion of glucose being 187 milligrams as compared with 130 milligrams in a normal infant, but some workers find no defect in the ability of the marasmic infant to burn carbohydrate.

Celiac Disease.—Children with this condition show an increased tolerance giving perfectly flat curves.

Vomiting.—In vomiting other than cyclic vomiting, low blood-sugars are reported. Some workers have failed to find any constant relationship between the blood-sugar level and the onset of an attack of recurrent vomiting. Ross and Josephs found a blood-sugar of 37

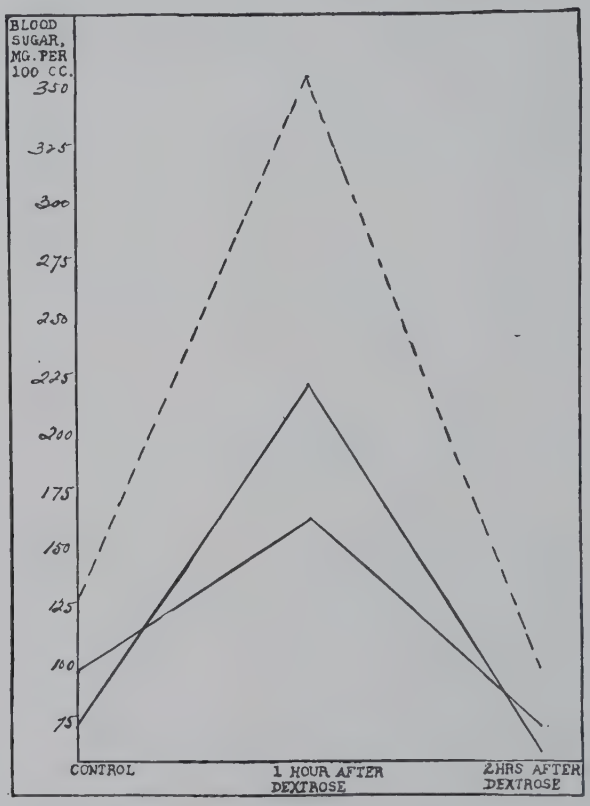


FIG. 27.—BLOOD-SUGAR CURVES FOLLOWING INJECTION OF 20 PER CENT DEXTROSE SOLUTION—20 C.C. PER POUND OF BODY WEIGHT.

The broken line indicates the control case, and the solid line, patients with celiac disease.

milligrams in a child during an attack, and during fasting this child's blood-sugar showed a greater decrease than did other fasting children. Attacks could be precipitated by fasting or a low carbohydrate diet and could be controlled by glucose administration.

Miscellaneous Conditions.—High blood-sugars are met with in tuberculous and other forms of meningitis, and tuberculous meningitis shows a decreased tolerance; hyperglycemia after convulsions is

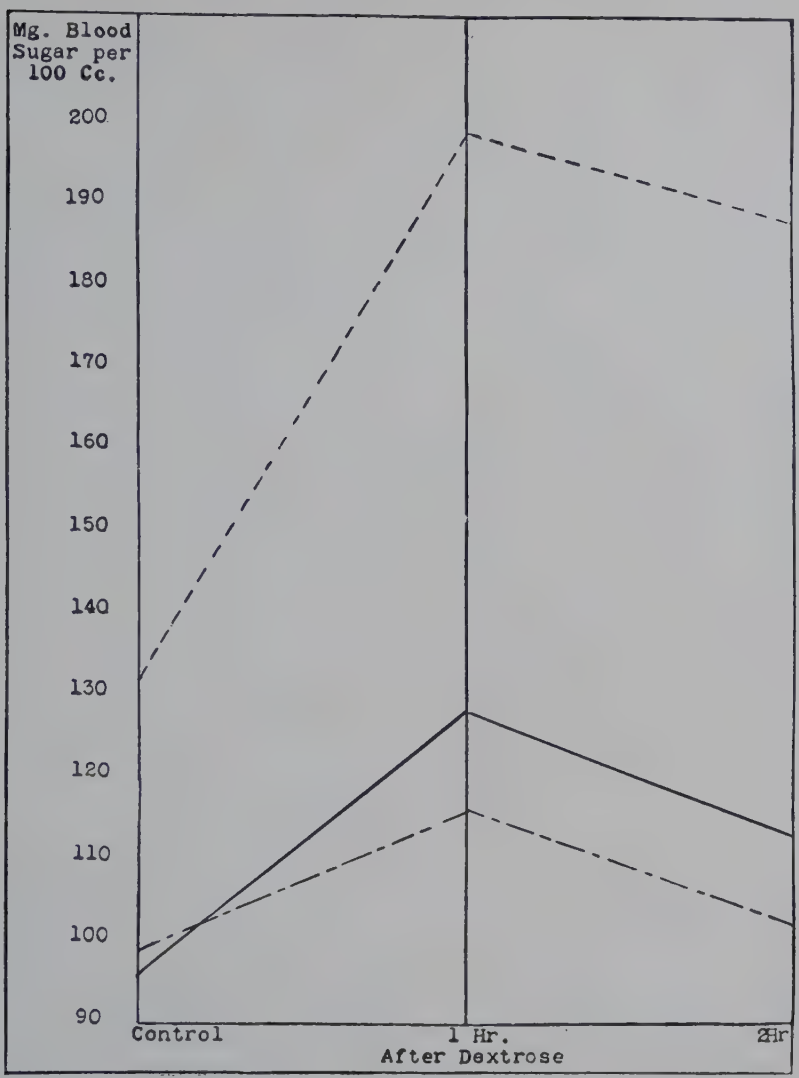


FIG. 28.—THE ALIMENTARY DEXTROSE TOLERANCE OF INFANTS WITH TUBERCULOUS MENINGITIS (BROKEN LINE) AND OF INFANTS WITH EPIDEMIC ENCEPHALITIS (DOT-DASH LINE), AS COMPARED WITH THAT OF NORMAL INFANTS (SOLID LINE).

common. Cases of intestinal intoxication show blood-sugar slightly above normal during fasting. Starvation lowers the blood-sugar in infants and children, figures as low as 45 milligrams being reported after short fasts. This tendency is less marked in the older children. After anesthesia hyperglycemia is found, and in some emotional dis-

turbances a hyperglycemia due probably to an endocrine dysfunction has been observed. In convulsions occurring at the onset of acute infections, low blood-sugars have been found and glucose therapy is of some benefit. McLean and Sullivan have found a low blood-sugar in cases dying a status thymicolymphaticus death. These workers think the hypoglycemia indicates an acute suprarenal insufficiency which is the cause of death.

Renal Diabetes.—This is a condition in which we have glycosuria with a normal blood-sugar content, *i.e.*, the renal threshold for sugar

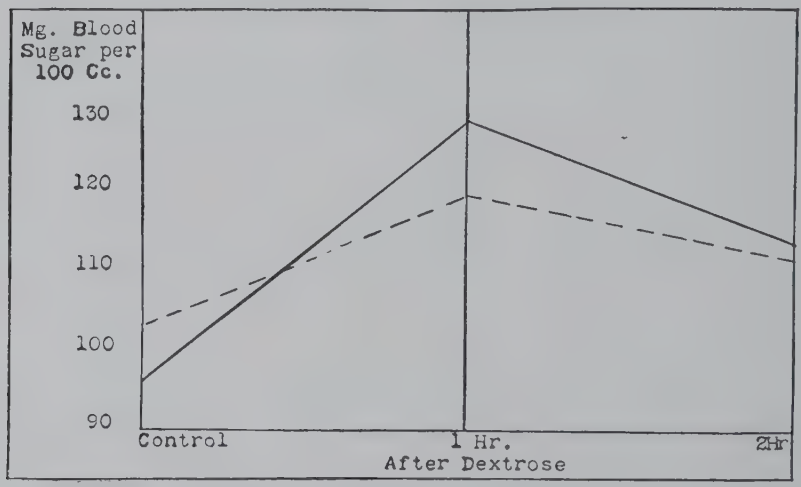
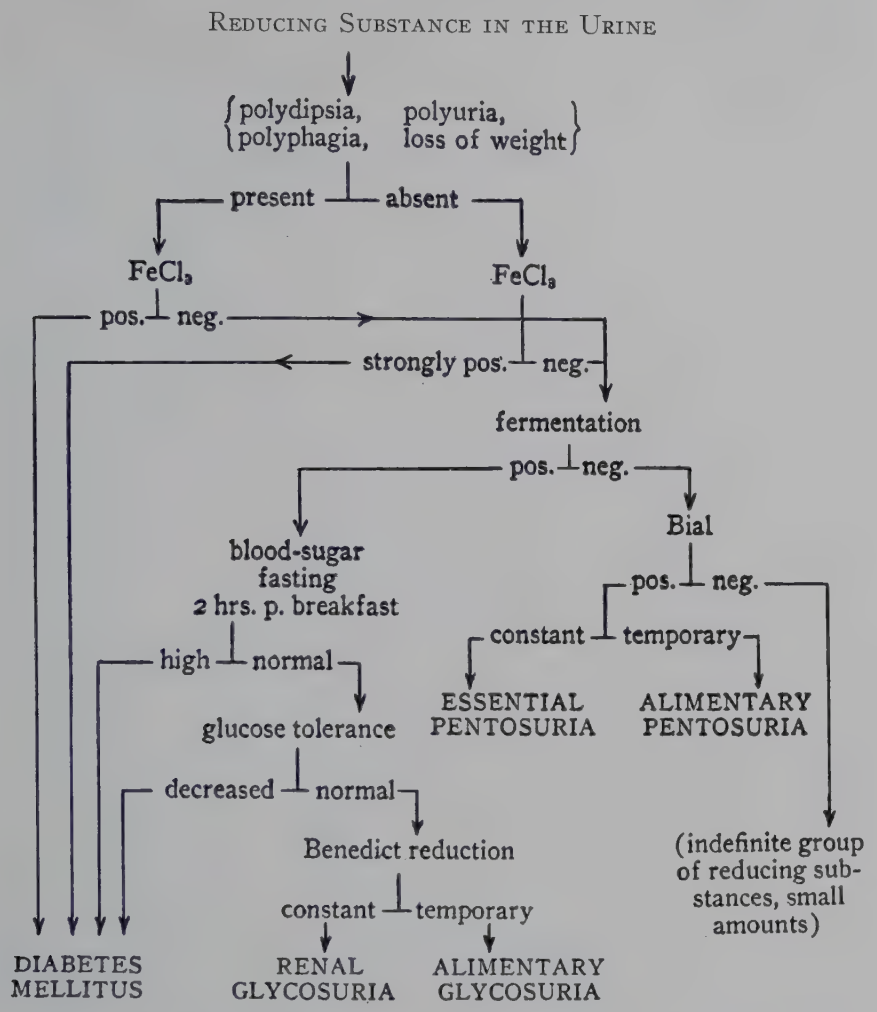


FIG. 29.—THE ALIMENTARY DEXTROSE TOLERANCE OF INFANTS WITH TETANY (BROKEN LINE), AS COMPARED WITH THAT OF NORMAL INFANTS (SOLID LINE).

is lowered. The diagnosis is made when we prove that the reducing substance in the urine is glucose, and the blood-sugar is within normal limits.

Outline of Work-up for Cases of Glycosuria.—Having an indulgent patient whose urine reduces Benedict's reagent, one is able to arrive at the correct diagnosis easily and rapidly by following the schematic outline below. The ferric chlorid, fermentation, and Bial tests are simple procedures. The materials to determine the blood-sugar are also necessary. Such a patient should be considered a diabetic until proven otherwise, but it is highly dangerous and unfair to treat the other possible conditions as if diabetes were present. It is not necessary to stress the importance of early diagnosis.



This outline concerns itself only with diagnosis and does not include the necessary data to determine the severity of the disease. No account is taken of perfectly obvious conditions such as the end stages of tuberculous meningitis which may give rise to a glycosuria. The osazones and their melting-points and other confirmatory tests are not included because they are unnecessary though satisfying.

For all practical purposes, a substance reducing Benedict's reagent is either glucose or a pentose. Levulose occurs with glucose, but rarely is found without it. Lactosuria is found in very young infants and lactating women.

The glucose tolerance test no longer occupies the place of prominence in diabetes which it formerly did. The results may be confusing. A blood-sugar during fasting and another determination two hours after an average breakfast usually give much more information. The tolerance test as used here is the final barrier to entering the group of innocent glycosurias and is rarely necessary in making the diagnosis of diabetes.

No quantitative determinations are necessary or helpful in arriving at the diagnosis. Renal glycosurias may average 5 per cent for years and pentosurias may completely reduce the copper solution.

Renal glycosurias and the pentosurias are asymptomatic and merit no treatment. The alimentary glycosurias always remain under a faint cloud of suspicion.

DISTURBANCES OF ACID-BASE EQUILIBRIUM

Acidosis.—Acidosis is an abnormal condition due to the formation or absorption of acids at a rate exceeding their elimination or combination with buffer. As defined by Van Slyke, it is a condition caused by acid retention sufficient to lower either the bicarbonate or the P^H of the blood below normal limits. It is never a primary condition, but always secondary. True acidosis with increased hydrogen-ion concentration (P^H below 7.3) is not common, although it probably occurs more often than was at first thought possible. Clinical acidosis where the alkali reserve is lowered (carbon dioxid combining power below 40 vol. per cent) is common.

Means classified acidosis as follows:

1. Metabolic, of which diabetes is an example.
2. Alimentary, where acids are ingested.
3. Retentive, as in the terminal stages of nephritis.

Or they could be grouped according to the cause of the acidosis:

1. Ketosis overproduction and accumulation of ketone bodies.
2. Lactic acid acidosis—overproduction and accumulation of lactic acid.
3. Renal insufficiency—failure of the kidneys to excrete acid phosphate and other acids.

4. Loss of alkali—in severe diarrhea an acidosis may be caused by loss of alkali through the bowel.

It is rare to find any of these conditions existing in a pure form. Diabetic acidosis or ketosis is frequently complicated by poor kidney function. Infants with loss of base through a diarrhea sometimes have in addition a ketosis caused by an infection. Other conditions where acidosis exists are also probably mixed.

Hydrogen-Ion Concentration of the Blood.—Normally the reaction of the blood is slightly alkaline, the P^H varying between 7.3 to 7.5 and is markedly constant in health. It is doubtful if the man in practice will have occasion to do P^H on the blood of infants and children. Yet an outline of the mechanism by which the acid-base equilibrium is maintained is necessary if one wants to understand and treat conditions in which acidosis and alkalosis occur.

Acid-base equilibrium is maintained by a combination of neutralization and excretion. Normally acid substances are ingested and formed in excess of base. In spite of this, a normal P^H is maintained except in the terminal stages of certain diseases. The mechanism by which this is done is somewhat as follows:

Neutralization of Acids by Body Bases.—Ammonia.—This is derived from waste nitrogen and would ordinarily be excreted as urea. It acts in an indirect way to help preserve equilibrium. The acid bodies while circulating in the blood are neutralized by fixed base, but as they pass through the kidney ammonia is substituted for this fixed base and they are excreted as ammonium salts. In this way large amounts of base are conserved to the organism.

Fixed Base.—Sodium, potassium, calcium and magnesium are the other bases used to bind excess of acid. It is not to be understood that all of these bases are available for use since a great many of them are bound up with body structure, or with strong acids and cannot be taken away if life is to continue. But a certain amount of fixed base is present in the circulating blood for the purpose of neutralizing acid. (See Gamble, Ross and Tisdall.) The most important part is the base bound as bicarbonate which can be used to neutralize any strong acid, carbonic acid being freed. So important is this bicarbonate that it is regarded as the alkaline reserve of the plasma and its estima-

tion gives us the best index of acid-base equilibrium. It is estimated by determining the carbon dioxid combining power of a small amount of plasma (the gas given off by adding strong acid to plasma saturated with carbon dioxid, and creating a vacuum is the carbon dioxid derived from the decomposition of bicarbonate) and is expressed as c.c. of carbon dioxid yielded by 100 c.c. of plasma. For the normal adult it varies between 52 and 75 c.c. per 100 c.c.; in infants and children it varies between 42 and 65 c.c. per 100 c.c.

Excretion of Acids.—Lungs.—Any decrease in the acidity of the blood at once stimulates the respiratory center to increase pulmonary ventilation (hyperpnea) and an increased amount of carbonic acid is given off. Acetone and volatile acids can also be excreted in this way. Any decrease in the acidity of the blood is met with by diminished pulmonary ventilation and a piling up of carbonic acid in the blood.

Kidney.—The chief action of the kidneys is to eliminate acid phosphate. This response is not so prompt as that of the lungs.

Two other reactions occur within the system which aid in maintaining the P^H of the blood at a constant level. They will only be mentioned here. They are the oxyhemoglobin-hemoglobin change and the chlorid shift. The most important factors are the neutralization of acids by base and the excretion of acids by lungs and kidney. But it must be remembered that other mechanisms are functioning.

Briefly then, the maintenance of a normal P^H depends on the relationship of two variable factors, the alkaline bicarbonate, $BHCO_3$ (when B indicates any monovalent base as Na, or K) and carbonic acid, H_2CO_3. If both factors increase in the same ratio there will be no change in the P^H. A rise in the carbonic acid content, the bicarbonate remaining the same, causes a drop in P^H, and we have an acidosis—uncompensated type. If, on the other hand, we have a drop in the bicarbonate, and the neutrality regulating mechanism is functioning properly, the carbonic acid drops in proportion, we have an acidosis of the compensated type without change in the P^H.

If hydrochloric acid is added to plasma, chlorids are formed, carbonic acid and acid phosphate are liberated. Plasma is a buffered solution, that is, the presence of the salts of weak acids as the bicarbonate and phosphates diminishes the change in the reaction of a fluid produced by adding a strong acid. Strong acids dissociate entirely, and

weak acids dissociate very little. So the presence of these weak acids produces only a slight increase in the hydrogen-ion concentration as compared to the presence of an equal amount of a strong acid. Following this buffering action, the weak acids formed are quickly excreted, acid phosphate being put out by the kidney and carbonic acid going off through the lungs. It will be seen how important the bicarbonate is in this mechanism since most of the base available for binding strong acid exists in this form.

Van Slyke has summarized the possible variations in acid-base equilibrium as follows:

1. $NaHCO_3$ increased. H_2CO_3 not increased to same extent. P^H raised. Seen in overdosing with bicarbonate and in excessive loss of HCl by vomiting. Bicarbonate excreted by kidney, ammonia disappears from urine.

2. $NaHCO_3$ increased. H_2CO_3 increased to an equivalent extent. P^H normal. In alkali administration in moderate dosage.

3. $NaHCO_3$ normal. H_2CO_3 normal. P^H normal. In health.

4. $NaHCO_3$ diminished. H_2CO_3 correspondingly diminished. P^H normal. In diabetes, nephritis, and diarrheal acidosis of infancy. Urinary ammonia and acid phosphate increased.

5. $NaHCO_3$ diminished. H_2CO_3 not correspondingly diminished. P^H low. In diabetes and nephritis premortal stage. Urinary ammonia and acid phosphate increased.

6. H_2CO_3 increased. $NaHCO_3$ not increased to same extent. P^H low. Observed in conditions in which the respiratory center is rendered insensitive by narcotics (e.g., morphia), or produced by breathing air containing excess of CO_2. Increased urinary excretion of ammonia and acid phosphates.

7. H_2CO_3 increased. $NaHCO_3$ increased to equivalent extent. P^H normal. In emphysema and cardiac disease.

8. H_2CO_3 diminished. $NaHCO_3$ correspondingly diminished. P^H normal.

9. H_2CO_3 diminished. $NaHCO_3$ not correspondingly diminished. P^H raised. In oxygen want, voluntary hyperpnea, and prolonged hot baths.

Ammonia excretion diminished, and some bicarbonate excreted, but less than in 1.

Symptomatology.—Acidosis presents a variable clinical picture, but the common symptoms when this condition is developing or has developed are as follows: Apathy and lassitude with periods of irritability, loss of appetite, nausea and vomiting, weakness, dehydration with loss of skin turgor, loss of conjunctiva luster, dry cherry-red lips, drowsiness, hyperpnea, and poor kidney function. Hyperpnea, the rapid pauseless respiration, is one of the most important signs.

Ketosis.—Normally fat is oxidized completely. Late in the process it becomes beta-oxybutyric and aceto-acetic acids. If enough sugar is burned it forms a product which can be readily broken down to carbon dioxid and water. If enough sugar is not metabolized or available, the products of incomplete oxidation of fat will accumulate. When large amounts are formed and cannot be excreted fast enough, an acidosis occurs, and the condition is called ketosis. In infants and children ketosis develops in greater or less degrees in the following conditions:

1. Starvation
2. Vomiting
3. Diarrhea
4. Acute infections
5. Ileocolitis
6. Ketogenic diet
7. Postoperative
8. Diabetes

Ordinarily a mild ketosis is not a serious condition, and a positive test for acetone and diacetic in the urine does not make a diagnosis of acidosis, or call for unusual therapeutic measures. But in a child very sick from any cause, if a condition of ketosis is added to an overburdened organism, it is a complication to be fought.

The laboratory work concerns the urine and blood. The usual qualitative tests for acetone and diacetic in the urine are reliable, and give some idea of the amount of ketosis present. But it must be remembered that ketones may be found in the urine while the blood content remains normal. Ketonuria does not always mean ketonemia.

Acetone bodies are present in the blood normally in small amounts from 3 to 8 milligrams per 100 c.c. In experimental work they can

be measured quantitatively, but for clinical work the qualitative test will do.

A moderate degree of ketosis may be present without lowering the alkali reserve. With severe degrees of ketosis the carbon dioxid combining power of the plasma is definitely low, an acidosis is present. There is, however, no close relation between the amount of ketone bodies present and the lowering of the alkali reserve. This suggests that some other factors are active in the production of the acidosis.

There is also no constant relation between ketosis or the blood-sugar level. Ketonuria may be present with low, normal or high blood-sugar.

Ketogenic diets are used as a form of therapy in epilepsy. In the normal adult ketosis will not occur when the fatty acid-glucose ratio is 0.75 to 1. Woodyatt has devised a formula for calculating this ratio.

It is well known that certain children have an increased susceptibility to ketosis. Schloss and Weymüller with increasing ketogenic diets found that these children developed a greater degree of ketosis and more easily than normal children. The mechanism of this is not known. These workers think that possibly the ketogenic action of a diet rich in fat is by the diversion and deposition of absorbed fat in the tissue. This shifting of fat seemed much less marked in the susceptible children.

In treating ketosis carbohydrate should be given by vein if necessary (5 per cent glucose). In order to make sure that the carbohydrate will be utilized, insulin, 1 unit, to 4 or 5 grams of glucose can be given. If the plasma bicarbonate is very low, alkali can be given in the acute stage.

Lactic Acid Acidosis.—Lactic acid is produced from carbohydrate and is formed during the period of muscular contraction, and in other metabolic processes. Normally, part of it is broken down to carbon dioxid and water and part is resynthesized. This is done promptly if circulation and pulmonary aëration are normal. But lactic acid will accumulate in sufficient quantity to lower the alkali reserve in conditions of anhydremia and impaired circulation. Cardiac decompensation, pulmonary conditions, the blood concentration following burns, anhydremia due to fluid loss by mouth, or by bowels, are all condi-

tions in which the lactic acid acidosis is likely to occur. Treatment, of course, is directed to the primary condition and to overcoming the anhydremia.

The lactic acid content of the blood in normal children is from 10 to 30 milligrams per 100 c.c. In some cases of cardiac decompensation and alimentary intoxication with anhydremia it may go as high as 260 milligrams per 100 c.c., with the carbon dioxid combining power as low as 15 vol. per cent. Marriott warns against large doses of alkali in this type of acidosis because alkalosis is quite likely to develop.

Lactic-acid acidosis is met with in the following conditions in infants and children:

1. Dehydration from any cause.
2. Cardiac disease with decompensation.
3. Any condition where the respiration exchanged is interfered with as pneumonia, or injury to the respiratory center.
4. Great muscular activity as in convulsions.

Acidosis Due to Loss of Alkali.—In severe and prolonged diarrhea water is lost from the body. This results in a concentration of most of the solutes, hemoglobin, proteins, chlorids, etc. But base bicarbonate is not concentrated because a great deal of it is lost in the stools, and probably some of it goes out in the urine in the attempt to maintain a normal osmotic pressure of the plasma. In addition there is usually present an oliguria with poor kidney function, and changes in blood volume and circulation favor an accumulation of lactic acid which increases the acidosis. Thus the acidosis occurring in anhydremia while mainly the result of loss of base is made worse by oliguria, or actual kidney damage and the accumulation of lactic and other acids.

The blood changes in this type of acidosis are along the following lines: There is a marked reduction in the carbon dioxid combining power, figures as low as 10 vol. per cent being reported. This may be accompanied by a rise in the hydrion content, the P^{H} falling as low as 7. There is a concentration of protein up to 10 per cent. Inorganic phosphate is increased up to 8 to 10 milligrams per 100 c.c., and plasma chlorids may go as high as 650 milligrams. Lactic acid may accumulate up to 100 milligrams and non-protein nitrogen is sometimes as high as 150 milligrams.

The urine is variable. The specific gravity is high, it may be acid or alkaline; albuminuria, cylindruria, and cells are usually present. The urine picture may be that of a severe nephritis, and yet not much anatomic change is found at autopsy. Kenoturia is rarely found.

In treating these cases, the chemistry would indicate that the loss of water and base should be made up by forcing fluids, and sodium bicarbonate. Rectal and oral administration is not satisfactory, and fluid must be given by vein or by clysis or intraperitoneally. Saline is usually given, but as Marriott points out the results are bad since we have a retention of salt, and poor kidney function prevents adequate urinary excretion of salt. Salt retention is followed by secretion of bicarbonate in the urine, and the acidosis is increased. It is better to give isotonic glucose (5 per cent) intraperitoneally or by vein. Sodium bicarbonate should also be given to keep up the carbon dioxid combining power. Fluid administration also tends to restore normal blood volume and circulation, and favors the removal of lactic acid.

Acidosis in Nephritis.—A moderate ketosis may accompany acute nephritis in children especially at the onset if infection is present, or there is vomiting. This is not usually serious.

In acute glomerular nephritis with uremia, a definite acidosis is usually present. The increased muscle contractions and anoxemia cause an accumulation of lactic acid. With poor kidney function there may be an increase in phosphate and other acid. Treatment here is directed toward stopping the convulsions and relieving the anoxemia. Hypertonic glucose or 1 per cent magnesium sulphate by vein will frequently relieve the cerebral symptoms, and help to restore normal acid-base equilibrium.

In chronic nephritis a severe acidosis frequently develops which is very difficult to treat. The hydrion concentration is increased, the P^H going as low as 7.2 and the carbon dioxid combining power is as low as 18 vol. per cent. Inorganic phosphate may go as high as 16 milligrams, and lactic acid is increased as are other unknown acids. Nitrogen retention is marked, non-protein nitrogen going as high as 200 to 400 milligrams. Another factor in the production of acidosis in nephritis is the loss of base due to failure of the kidney to substitute ammonia for fixed base. Little can be done to treat this type of acidosis. Alkali can be given by mouth or by vein, and calcium ace-

tate by mouth may cause an excretion of phosphate through the intestine. To a certain degree this acidosis may protect the organism against the development of tetany, and in chronic nephritis a more or less severe acidosis may last for years.

Alkalosis.—*Symptomatology.*—Mild forms of alkalosis are not easily recognized. The conditions should always be looked for when bicarbonate is being administered over any period of time. The respiration is low, shallow, and irregular with periods of apnea quite in contrast to the respiration af acidosis. Other signs are headache, nausea, and vomiting. Severe degrees of alkalosis show signs of tetany as neuromuscular irritability, tingling, carpopedal spasm, Chvostek's and Trousseau's sign, convulsions and coma. Practically all of the symptoms developing in acidosis can appear in alkalosis. The chief difference is in the respiration.

Diagnosis rests on the determination of the carbon dioxid combining power which may go as high as 100 vol. per cent, and a determination of the P^H of the blood, which may reach 7.8.

The urine becomes alkaline and contains little or no ammonia since it is not needed to save the base, and no phosphate is put out.

In infants and children alkalosis is most often met with in upper intestinal obstruction as pyloric spasm, stenosis, or where vomiting has been persistent and prolonged from any cause. The laboratory findings are concerned chiefly with the blood chemistry and urine. The blood shows a concentration with high hemoglobin and high serum protein. There is also a severe degree of nitrogen retention, both urea and creatinin being elevated, chlorids are low. There is an increase in the alkali reserve, the carbon dioxid combining power going as high as 80 to 90 vol. per cent. The clinical manifestations of severe alkalosis, convulsions and tetany are usually present. Albuminuria with casts and cells are found, and autopsy shows a tubular degeneration or a diffuse nephritis. The indications are for the clinician to combat the concentration and alkalosis by forcing fluids, administration of chlorids, and the inhalation of $CO_2 — O_2$ mixture. Bicarbonate is, of course, contra-indicated. Kidney function is also helped by these measures.

We also find alkalosis in cases of epidemic encephalitis where the respiratory center is damaged, lung conditions which result in lowered

oxygen intake, forced ventilation, or overbreathing for any cause, and overdosage with alkali. In fever with increased pulmonary ventilation, alkalosis frequently develops. Carbon monoxid poisoning will also cause alkalosis.

BLOOD CHANGES IN TETANY AND RICKETS

The only constant and significant finding in blood of patients with infantile tetany is the reduction in the calcium concentration of the serum. Except in nephritis the demonstration of the serum calcium below 7 milligrams per 100 c.c. means tetany whether latent or manifest. This fact was first demonstrated by Howland and Marriott, and later confirmed by other workers.

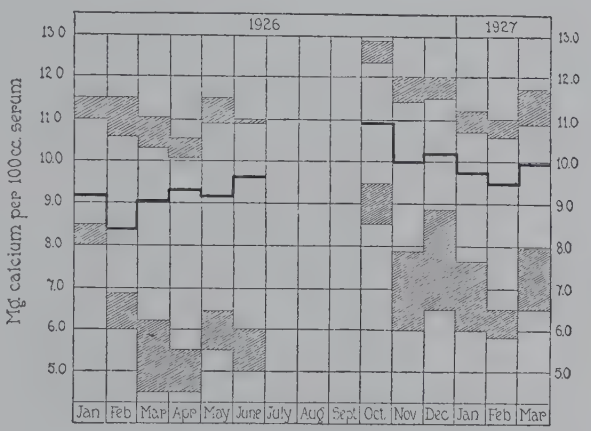


FIG. 30.—SEASONAL VARIATION IN THE SERUM CALCIUM OF INFANTS.

The heavy line represents the medians for the various months; the upper and lower cross-hatched areas, the uppermost and lowermost 10 per cent of all determinations for each month. (From Am. J. Dis. Child., December, 1927.)

It is now generally conceded that the calcium is contained entirely in the plasma, and that the cells are free from calcium. The calcium in health is singularly constant, not only for man but for various animals as well. In normal infants the calcium varies between 9.5 and 12 milligrams per 100 c.c. of serum. In the newborn the values are slightly higher (10.5 to 12). Grant and Gates note a seasonal variation in the calcium level in rabbit's blood with peaks in May and November, and low levels in January. Bakwin showed a drop in calcium values from January to March with a rise into the summer months, and a fall beginning in November. They attribute the changes to variations in ultraviolet radiation, and the large number of infections during the winter months.

In infants with tetany the values are below 7.5 milligrams and

usually between 5 and 6 milligrams per 100 c.c. of serum. Values as low as 3.5 milligrams have been obtained. Griffith has recently reported cases of tetany in which the calcium values of the serum were normal. These cases must be very rare.

Other changes may occur in the blood of infants with tetany, but they are inconstant and of no clinical significance. An increase in the serum potassium has been occasionally observed. There is no change in the blood carbon dioxid, P^H, sodium, or magnesium. The serum proteins are also unchanged. The organic phosphorus tends to be higher

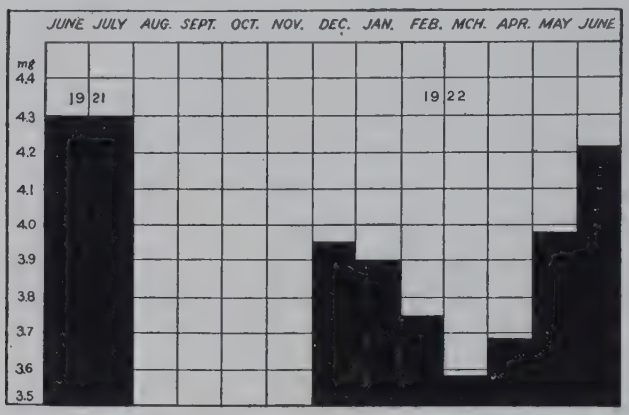


Fig. 31.—Seasonal Tide of Blood Phosphate (Inorganic).
(From J. Am. M. Ass., December, 1922.)

than normal, but when the tetany is associated with acute rickets, it may be normal or subnormal.

In infants with tetany the inorganic phosphorus of the blood is not significantly altered while the calcium of the serum shows a regular and marked fall. In rickets, on the other hand, the calcium content of the serum remains unchanged, but the inorganic phosphorus falls. This observation was made simultaneously by Howland and Kramer.

In normal infants under two years the concentration of inorganic phosphorus in the serum is about 5 milligrams per 100 c.c. It is slightly higher in the blood of the newborn, and is much lower in the blood of adults (about 2 milligrams). In infants with active rickets the inorganic phosphorus is regularly reduced below 3 milligrams per 100 c.c. During healing the inorganic phosphorus rises to normal.

It has been frequently stated that rickets is an acidosis condition,

but there is no change in the blood to indicate this. As noted before, there is a seasonal variation in the phosphate in infants. From a maximum of 4.5 in June, it falls to 4 milligrams in December, and to 3.5 milligrams in March.

Late or juvenile rickets has been described. Following the World War many cases were reported from Germany. According to Hess, it occupies a place between rickets in infants and osteomalacia in adults. Hess also says there is "an unbroken and insensible transition between late rickets and osteomalacia." Not a great deal is known about the etiology and laboratory findings in rickets developing from insufficient diet. Celiac rickets is probably due to calcium loss; low calcium in the diet, and excessive calcium loss in the fatty stools. The blood calcium is low and the phosphate normal or high. Renal rickets is described under nephritis.

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